THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY

CHENNAI – TAMILNADU

DISSERTATION

ON

"A STUDY ON CORRELATION BETWEEN SERUM CORTISOL AND EARLY STROKE OUTCOME"

SUBMITTED FOR M.D. DEGREE EXAMINATION

BRANCH I

(GENERAL MEDICINE)

EXAMINATION IN

APRIL – 2014

TIRUNELVELI MEDICAL COLLEGE

TIRUNELVELI

CERTIFICATE

This is to certify that this dissertation work entitled **"A STUDY ON CORRELATION BETWEEN SERUM CORTISOL AND EARLY STROKE OUTCOME"** is the bonafide record work done by Dr JOSE SEBASTIAN PAIKADA**,** submitted as partial fulfillment for the requirements of M.D. Degree Examinations, General Medicine (Branch I) to be held in APRIL 2014.

Prof. DR. A.S. MOHAN M.D.
Professor of Medicine
Unit Chief III Medical unit
The Department of Medicine
Tirunelveli Medical College Hospital
Tirunelveli.

Prof. Dr. R. GEETHARANI M.D
Professor and H.O.D,
The Department of Medicine
Tirunelveli Medical College Hospital
Tirunelveli.

THE DEAN

Tirunelveli Medical College Hospital

Tirunelveli.

TIRUNELVELI MEDICAL COLLEGE

TIRUNELVELI,

STATE OF TAMILNADU, INDIA

PIN CODE:627011

Tel: 91-462-2572733, 2572734 Fax: 91-462-2572944

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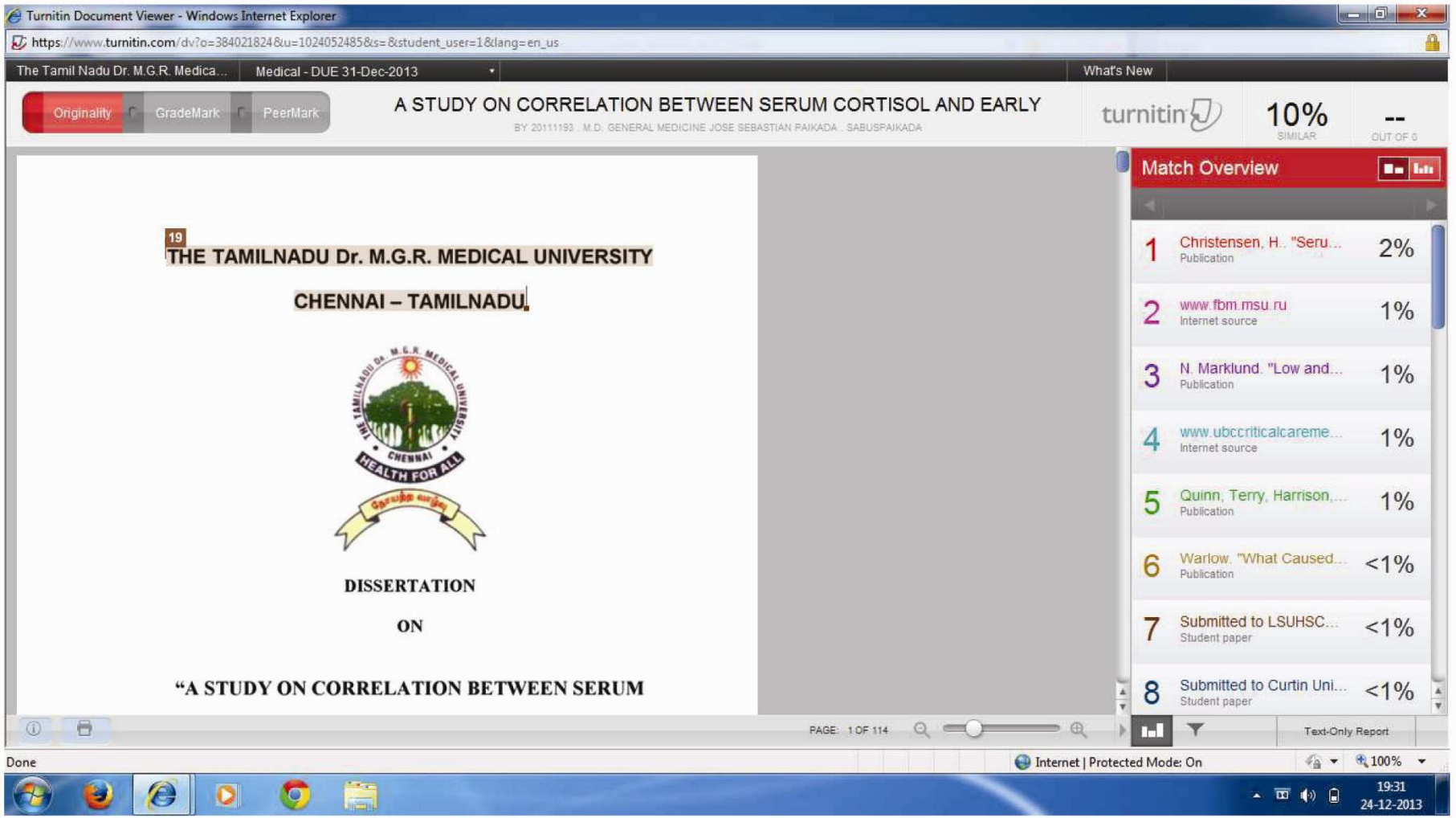
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I **Dr.JOSE SEBASTIAN PAIKADA** solemnly declare that this dissertation work titled **"A STUDY ON CORRELATION BETWEEN SERUM CORTISOL AND EARLY STROKE OUTCOME"** is a bonafide one done by me at **TIRUNELVELI MEDICAL COLLEGE HOSPITAL** during 2012-13 period under the guidance and supervision of my unit chief **PROF. DR. A. S. MOHAN, M.D.**

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Place : Tirunelveli

Date : **Dr. JOSE SEBASTIAN PAIKADA**

ACKNOWLEDGEMENT

I am greatly indebted to my unit chief and guide **Prof.Dr ARUMUGAPANDIAN @ S. MOHAN M.D,** who inspired, encouraged and guided me in every step of this study.

I express my heartfelt gratitude to the professor and Head of the Department of medicine **Prof. Dr R.GEETHARANI M.D.** for her valuable support and guidance in preparing this dissertation.

I am extremely thankful to **DR. S.SOUNDARARAJAN M.S.,** Dean of Tirunelveli Medical College for granting me permission to do this dissertation work in Tirunelveli Medical college Hospital, Tirunelveli.

I am thankful to the Assistant Professors of my unit.

Dr. PERIASAMY M.D. Dr.A.RAJESH M.D and Dr.MARCHWIN KINGSTON M.D., for their guidance and help throughout my dissertation work.

I thank the Department of Radiology and Biochemistry for their help in investigation aspects.

I express my gratitude to all patients participated in this study.

CONTENTS

INTRODUCTION:

Stroke is a common neurological disorder in clinical practice causing death in the developing countries as well as developed countries.Stroke is defined as an acute neurological injury occurring due to vascular pathological processes which manifest either as brain infarction or hemorrhage. Risk factors can never explain the timing and activity of the occurrence of stroke. But we can prevent the onset of stroke by reducing the risk factors.

A stress response occurs after stroke which causes increased levels of cortisol and catecholamines[1] .This has been known since the 1950s. There is also a dysregulation of the hypothalamo- pituitary- adrenal (HPA) system which is shown by a failure of the dexamethasone suppression of cortisol levels,in stroke.This cortisol response to stroke has been identified in both cerebral infarction as well as in intracerebral haemorrhage[2] of any cause.

The high s-cortisol levels have been related to the severity and adverse clinical and functional outcome[3] in stroke. But it has not yet been proven whether this glucocorticoid response to stroke gives beneficial or harmful effect to the already damaged brain.

This cortisol response in stroke is related positively to blood glucose[4] which increases after a cerebrovascular accident. It has also been found that cortisol levels correlated positively to the white blood cell

counts, fibrinogen levels, and other markers of inflammatory and immune response which occurs after stroke[5]. This includes IL-6[6] as well. It is also suggested that cytokines will modulate the cortisol response after stroke by stimulating the hypothalamo - pituitary axis leading to an increased levels of serum cortisol[7].

Some researchers have suggested that the less favourable outcome seen in stroke with increased levels of stress-hormones could be related to cardiac abnormalities. In one study, degree of the sympathetic activation seen in stroke was associated with the extent of damage to the insula. It is assumed that insula is involved in the regulation of autonomic nervous system[8]. It has been shown that insular damage in experimental stroke resulted in an increase in the circulating catecholamine levels suggesting this as the mechanism for cardiac complications seen with stroke[9]. It has been observed that the normal circadian rhythm of cortisol secretion is lost during acute stroke, as equal serum cortisol levels were found round the clock[10].

It remains uncertain whether this stress response to stroke is just an epiphenomenon to stroke severity or it independently contributes to prognosis and functional outcome . Furthermore, till now the stress response has not been correlated with the clinical and biochemical variables generally assumed to be of importance in a case of cerebrovascular accident.

AIM OF THE STUDY

1. The aim of the study is to investigate if a single serum cortisol level determination could predict the outcome of stroke.

2. Whether serum cortisol as well as stroke severity is related to any clinical or paraclinical parameters of known relevance in acute stroke.

3. To gain knowledge of the level of correlation between various clinical and paraclinical parameters (BP, Blood sugar and total count) with serum cortisol and stroke severity.

REVIEW OF LITERATURE

The normal functioning of brain is dependent upon a constant supply of glucose and oxygen. This is derived from the blood which perfuses it . About 55 to 70 ml of blood perfuses 100 gram of brain per minute. The source of energy for the brain tissue is almost exclusively due to oxidation of glucose.

Stroke also known as cerebrovascular accident is a spectrum of rapidly developing clinical symptoms and signs of focal or global (this is applicable to patients in deep coma) loss of brain function[11],and the symptoms lasting for a period of more than 24 hours or may lead to death, without any apparent cause other than a vascular[12] pathology. There occurs a wide range of severity in stroke ranging from recovery in a few days, to a persistent disability or death.

A TIA or transient ischaemic attack is defined as an acute transient loss of focal brain function, or monocular function with symptoms lasting for less than 24 hours. This is thought to be as a result of decreased cerebral or ocular blood flow which may be due to arterial thrombosis / embolism. This can also occur in situations of inadequate blood flow associated with cardiac or haematological diseases[13].

A RIND or reversible ischaemic neurological deficit refers to resolution of neurological deficit within a period of 7 days.

Regarding the incidence of various strokes, most common is ischaemic stroke coming to about 80 percent of all strokes.this is followed by primary intracerebral haemorrhage at 10 percent. About 5 per cent are due to subarachnoid haemorrhage.

In the developing world[14]stroke is the third most common cause of death. This comes after coronary artery heart diseases and all the cancers. An estimate of stroke prevalence is at about 5/1000 population, but the exact figure depends on age and sex structure of the given population and it comes at about 50/1000 in men, 25/1000 in women[15] . This applies to an age group of 65-74 yrs.

South Asian populations[16] have a high stroke mortality which is understandable by the high prevalence of coronary artery heart disease,increased waist to hip ratio ,central obesity , insulin resistance, non-insulin-dependent diabetes, and hypertension in them. This may be due to the genetic susceptibility and high serum lipoprotein (a) levels in these populations, potentiated by the diet and lifestyle induced changes in lipid levels[17].

Risk factors associated with ischaemic stroke are :

- ✓ Increasing Age
- ✓ Male sex
- ✓ High blood pressure
- ✓ Cigarette smoking
- ✓ Hyperlipidaemic state
- ✓ Diabetes mellitus
- ✓ High plasma fibrinogen levels
- ✓ Increased factor VII coagulant activity
- ✓ Raised tissue plasminogen activator antigen
- ✓ Decreased blood fibrinolytic activity
- ✓ Increased von Willebrand factor levels
- ✓ Raised blood haematocrit
- ✓ Atrial fibrillation
- ✓ Increased serum Sex hormone levels
- ✓ Excessive use of alcoholic beverages
- ✓ Obesity and high calory diet
- ✓ Physical Inactivity and lack of exercise
- ✓ Increased white blood cell count
- ✓ Recent or chronic Infections
- ✓ Hyperhomocysteinaemia
- ✓ Snoring and obstructive sleep apnoea

- ✓ Corneal arcus
- ✓ Depression and other Psychological factors
- ✓ Low serum albumin levels
- ✓ Diagonal earlobe crease
- ✓ Impaired ventilatory function of lungs
- ✓ Family history of cerebrovascular accident
- ✓ Evidence of pre-existing vascular and cardiac diseases
- ✓ Myocardial infarction
- ✓ Cardiac failure
- ✓ Peripheral vascular diseases
- ✓ Cervical arterial stenosis (presence of carotid bruit)
- ✓ Transient Ischaemic attacks

Age

It is a well established fact that age is one of the strong risk factors for development of ischaemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage[18].

Sex

There is a slight male preponderance which is most prominent in middle to old age, which disappears in the very elderly absent in the young.

Blood pressure

It is seen that, high blood pressure is strongly associated with increased stroke risk in both males and females . Though most of the information regarding blood pressure and stroke comes from consideration of the diastolic blood pressure, the risk of stroke with systolic blood pressure is similar and possibly stronger. It is thought that even 'isolated' systolic hypertension is associated with increased risk[19].

This association observed between increasing blood pressure and stroke is more evident in middle age than in elderly. It is not quite clear whether hypertension still plays a significant role in stroke occurring in very elderly individuals, where stroke may be associated with low pressures, because of low perfusion pressures which may be inturn due to reflection of pre-existing cardiovascular and other diseases.

Hypertension increases stroke risk by probably increasing the extent of atheroma[20] as well as its severity. The prevalence of small vessel disease in the perforating arteries within the brain increases with hypertension.

Cigarette smoking

Cigarette smoking is accepted more as a risk factor for coronary artery heart disease than stroke.But however there is no doubt that cigarette smoking has an association with stroke, which comes in a dose-responsive manner. Males and females are affected by smoking in

equal proportions, and the association seems to become weaker as the age progresses.There is perhaps an association with passive smoking[21] also.

Smoking is an established risk factor for subarachnoid haemorrhage and also for ischaemic strokes, but the association with primary intracerebral haemorrhage[22] seems to be less severe. Ex-cigarette smokers who have already stopped smoking have a persistent increased risk of stroke for the following few years as well.

Blood lipids

The relationship between blood lipids and stroke is much weaker, if at all it exists[23,24]. This is in sharp contrast to what is seen in coronary artery heart disease. But Increased serum lipoprotein (a) is predictive of stroke as shown by some studies. There has been some attempts to relate atheroma volume in the extra and intracranial circulation to the blood lipid concentrations and have suggested some association.

Diabetes mellitus

Diabetes mellitus is a strong causative factor for various micro and macro vascular diseases which has been recognised for long, and the risk is double as compared with non-diabetics, and this is probably independent of other risk factors such as hypertension[25].

Pathophysiology of acute cerebral ischaemia

Normally the brain derives its energy needs from the oxidative metabolism of glucose. But the glucose stores in brain is negligible. So when cerebral blood flow falls beyond a certain limit the brain becomes ischaemic, and a series of neurophysiological functions , which are dependent on the oxidative metabolism of glucose to provide energy in the form of ATP, are affected before cell death occurs.

Different mechanisms have been postulated which are responsible for the reversible loss of cellular function, and for irreversible cell death, that occurs in ischaemia.There are differences between the mechanisms that cause death of neurons, glial cells, and endothelial cells,and perhaps between the white matter and grey matter[26].

Cerebral ischaemia causes not only the reversible and irreversible loss of brain functions , but it also results in cerebral oedema[27] . Ischaemic cerebral oedema is partly 'cytotoxic' and partly 'vasogenic'. Cytotoxic cerebral oedema usually starts within minutes of onset of stroke, and affects the grey matter more than that of white matter. This is due to the damaged cell membranes allowing intracellular water to accumulate.

Vasogenic cerebral oedema, usually starts rather later when compared to cytotoxic oedema . The onset being within hours of stroke onset and affects the white matter more than the grey matter . It is due to

the damaged blood-brain barrier allowing plasma and its constituents to enter the extracellular space. Ischaemic cerebral oedema reaches its maximum in about 2-4 days and then subsides gradually over the next two weeks.

Hyperglycemia is often associated with a poor clinical outcome after stroke. This is either because of the fact that the consequences of ischaemia are exacerbated in the presence of high blood glucose concentrations, which is mediated by excess lactate[28] production , or because hyperglycemia reflects the stress response,which inturn is due to the the severity of the initial stroke[29]**.** But for making this more clear trials of glucose lowering need to be done in acute stroke.

It is also found that fever is associated with a worse outcome in acute stroke and hypothermia with a better outcome, but like blood sugar more studies are warranted to make it clear that this association is not just a casual relationship, so that interventions in this regard would be worthwhile. Dehydration, raised haematocrit values , increased whole blood viscosity are other potential factors exacerbating stroke severity.

The causes of ischaemic stroke :

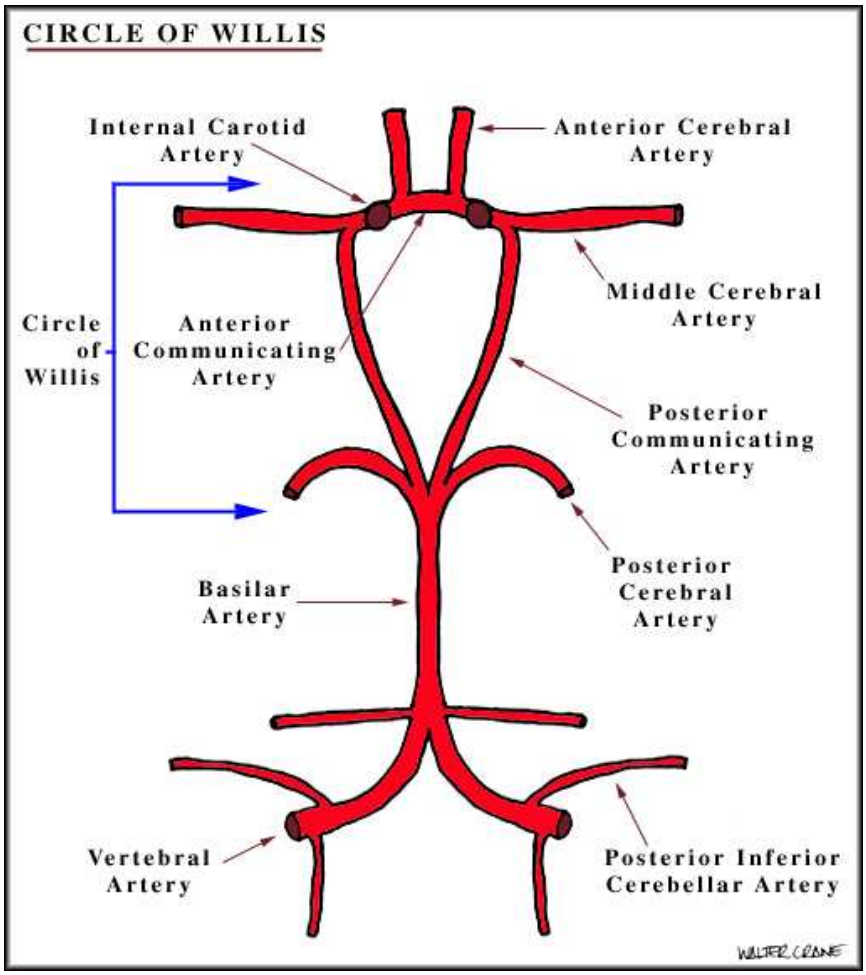
Cerebral ischaemia as well as infarction are usually caused by acute occlusion of an artery supplying the brain parenchyma ,or less frequently due to reduced flow distal to an already occluded or stenosed artery. Occlusion or stenosis of the vessel can be the result of diseases of

the arterial wall , embolism originating from the heart; haematological disorders, and various rare, but often treatable, conditions. Causes other than degenerative arterial disease is usually more common in young stroke patients.

The brain receives blood from two sources:

1. The internal carotid arteries , which arise at the bifurcation point of the common carotid arteries , and
2. The vertebral arteries.

   The internal carotid artery branches to give the anterior and middle cerebral arteries. The right and left vertebral arteries join to form the basilar artery at the level of pons. The basilar artery joins the branches of internal carotid system in an arterial ring called the circle of Willis at the base of the brain. The posterior cerebral arteries, anterior and posterior communicating arteries, arise at this confluence. Joining these two major sources of blood supply to brain through the circle of Willis, probably improves the chance of any part of the brain to receive its blood supply if one of the major arteries are occluded .



Causes of ischaemia and infarction of brain parenchyma:

- ✓ Arterial wall disorders
  - Atheroembolic occlusion
  - Intracranial small vessel occlusive disease
  - Infection
  - Trauma
  - Dissection of vessels
  - Fibromuscular dysplasia
  - various Congenital arterial anomalies
  - Moyamoya syndrome

- Leukoaraiosis
- Irradiation

- ✓ Embolism from the heart
- ✓ Haematological abnormalities
- ✓ Pregnancy and puerperium
- ✓ Oral contraceptive pills and female sex hormones
- ✓ Drug abuse
- ✓ Cancer associated
- ✓ Perioperative state
- ✓ Hypoglycaemia
- ✓ Migraine
- ✓ Inflammatory bowel diseases
- ✓ Hyperhomocystinaemia
- ✓ Fabry's disease
- ✓ Mitochondrial cytopathy
- ✓ Snake bite
- ✓ Fat embolism
- ✓ Nephrotic syndrome
- ✓ Epidermal naevus syndrome
- ✓ Susac's syndrome
- ✓ Fibrocartilaginous embolism
- ✓ Other Miscellaneous conditions

Atheroma is an inevitable accompaniment of ageing .This is particularly common in developed countries .Atheroma is the most common arterial pathology , and when it is superimposed by thrombosis or embolism as a complication, it becomes the most frequently encountered, but not the only cause of cerebral ischaemia and infarction.

The relative occurence of the important causes of ischaemic stroke and TIA is as follows:

- Atherothrombosis which affects medium as well as large-sized arteries between the heart and the brain : 50%
- Intracranial small vessel disease: 25%
- Embolism from the heart: 20%
- Rare disorders: 5%

Distribution of atheroma in the vessel

Atheroma usually affects the medium and large -sized arteries at places of arterial branching, confluence[30], and of tortousity. This is because these are sites of haemodynamic sheer stress and can cause endothelial trauma with boundary layer separation and blood stagnation.The accumulation of platelets and turbulence can promote thrombosis[31] . Atheroma usually starts in childhood, which is thought to be in response to endothelial injury[32]. The plaques are then complicated by platelet adhesion, followed by activation and aggregation. This results in blood coagulation and subsequent thrombosis.

Causes of dissection of the extra- and Intracranial arteries

- **TRAUMATIC**
  - Penetrating injuries
  - Non-penetrating Injuries
- **SPONTANEOUS**
  - Fibromuscular dysplasia
  - Inflammatory arterial diseases
  - Cystic medial necrosis of the arteries
  - Marfan's syndrome
  - Ehlers - Danlos syndrome
  - Infective arterial disease (e.g. syphilis)
  - Pseudoxanthoma elasticum

SPONTANEOUS INTRACRANIAL HAEMORRHAGE

Spontaneous intracranial haemorrhage usually occurs within the brain (primary intracerebral haemorrhage)or into the subarachnoid space which is called subarachnoid haemorrhage.

Intra cranial haemorrhage can also occur into the ventricles which is called intraventricular haemorrhage, and rarely into the subdural space (subdural haemorrhage). The exact site of origin may not necessarily be obvious immediately. This is because a saccular aneurysm can rupture into the brain parenchyma as well as into the subarachnoid space, or sometimes disruption of small perforating arteries can cause intraventricular as well as basal ganglia haemorrhage. There may be uncertainty even at post-mortem because the source of the initial haemorrhage may well have been destroyed, particularly if it is small like a tiny intracranial vascular malformation. But usually the causes of intracranial haemorrhage are almost the same, whatever the primary site of bleeding, may be,though their relative frequencies vary somewhat with the site of bleed.

Causes of spontaneous Intracranial haemorrhage:

- Hypertension
- Aneurysms
  - Saccular
  - Atheromatous
  - Myxomatous
  - Mycotic
  - Dissecting aneurysms
- Cerebral amyloid angiopathy
- Intracranial vascular malformation
  - Arteriovenous [cerebral and dural]
  - Venous malformation
  - Cavernous
  - Intracranial Telangiectasis
- Disorders of Haemostatis
  - Haemophilia and other disorders of coagulation
  - Thrombocytopenia
  - Thrombotic thrombocytopenic purpura [TTP]
  - Use of Anticoagulants
  - Thrombolytic therapy
  - Use of Antiplatelet drugs
  - Polycythaemia vera [PV]

- Essential thrombocythaemia [ET]
- Paraproteinaemias
- DIC/Disseminated intravascular coagulation
- Liver failure
- Renal failure
- Snake bite

❖ Inflammatory vascular diseases

❖ Haemorrhagic transformation of cerebral infarction

❖ CVT / cortical venous thrombosis

❖ Moyamoya syndrome

❖ Sickle-cell trait/disease

❖ Posterior fossa and other intracranial surgery

❖ Carotid endarterectomy

❖ Delayed post-traumatic 'spat-apoplexie'

❖ Wernicke's encephalopathy

❖ Alcoholic binge

❖ Vascular tumours

❖ Melanoma

❖ Malignant astrocytoma

❖ Choriocarcinoma

❖ Oligodendroglioma

❖ Haemangioblastoma

- ❖ Medullobiastoma
- ❖ Choroid plexus papilloma
- ❖ Bronchogenic carcinoma
- ❖ Endometrial carcinoma
- ❖ Hypernephroma
- ❖ Drug abuse
- ❖ Infections
    - ▪ Herpes simplex virus infection
    - ▪ Leptospirosis
    - ▪ Chronic meningitis
    - ▪ Anthrax
    - ▪ Scorpion bite
- ❖ Silastic dural implant

Primary Intracerebral haemorrhage [PICH]

Primary intracerebral haemorrhage (PICH) is more frequent than subarachnoid haemorrhage (SAH) and the incidence increases with age. It is primarily due to small vessel diseases of brain parenchyma associated with hypertension, cerebral amyloid angiopathy, and various intracranial vascular Malformations. But usually a combination of different factors may operate in a single individual for example, hypertension with cerebral amyloid angiopathy. Another example being

therapeutic thrombolysis done for STEMI in a patient who may be having an incidental intra cranial vascular malformation.

Less common causes may include intracranial saccular aneurysms , disorders of haemostatis, particularly induced by use of anticoagulants[33],thrombolytic therapy , and possibly use of antiplatelet drugs as well. Cerebral vasculitis and amyloid angiopathy are also rare causes of primary intra cerebral haemorrhage.

The site of PICH,as shown on a CT scan of brain,may provide some clue to the cause of the haemorrhage.

- 'hypertensive' haemorrhages occur slightly more in the basalganglia, thalamus, and the pons
- lobar haemorrhages which occur superficially in the cerebrum tend to be more often due to cerebral amyloid angiopathy, various vascular malformations, and due to disorders of haemostasis

Occasionally Primary intracerebral haemorrhages occur in different parts of the brain simultaneously. Rarely, PICH can be familial as well.

Spontaneous subarachnoid haemorrhage[SAH]

The occurence of spontaneous subarachnoid haemorrhage [SAH] actually increases with age and is about 5-10 per 100,000 population per year.it is somewhat more frequent in women than men. The most common cause of SAH is a ruptured saccular aneurysm[34] .

Some Subarachnoid haemorrhages are due to bleeding from an intracranial vascular malformation. A few SAHs are due to rarities, and in about 15 per cent no cause can be identified , depending on the intensity of investigations.

Except in premature babies, primary intraventricular haemorrhage is very unusual. In adults, a cause may not be always found and some may be due to vascular malformations in the ventricular wall[35] . The clinical features of primary intraventricular haemorrhage are so similar to SAH and can only be differentiated on a CT scan, or sometimes at post-mortem.

Subdural haemorrhages occur more often due to trauma , or due to ventricular decompression procedures for hydrocephalus, than spontaneous ones considering the fact that trauma can so easily be ignored or forgotten. Disorders of haemostasis , rupture of a vascular malformation in the dura or of a very peripheral vascular aneurysm of probably mycotic in etiology can lead to subdural haemorrhage as well. peripheral cerebral tumour can rarely be responsible for SDH. Subdural haemorrhage occurring as a very rare complication of lumbar puncture should not be forgotten.

Transient ischaemic attacks [TIA]

Roughly about 15 per cent of all first stroke patients have had earlier TIAs. But unfortunately only about half of them would have consulted a doctor. The annual incidence of TIA is about 0.5 per 1000 population. But this must be an underestimate of the real situation[36] because many patients with TIA will not consult a doctor . By definition, in TIA the symptoms last less than 24 hours. But a few patients may have residual neurological signs of no functional significance , such as a reflex asymmetry. About 25 per cent of patients with TIA may have focal hypodensity on CT, relevant to the symptoms of the patient and therefore indicates recent infarction[37].

An even higher proportion of patients will have focal lesions on MRI[38] scan of brain. But however, the diagnosis of TIA depends not either on neurological signs or imaging but essentially on the duration and nature of the symptoms in the background of vascular risk factors like absent pulses and bruits , particularly in an elderly patient. The neurological signs of TIA are likely to attenuate and disappear[39] but fortunately, there are only less inter observer disagreement about symptoms, in general , if at all any and are easily remembered . The main use of brain imaging in TIA is to rule out the very rare occurrence of 'transient focal neurological attacks' in structural lesions of brain.

Main causes of transient focal neurological attacks

- ✓ Focal cerebral ischaemia which is a TIA
- ✓ Migraine with aura
- ✓ Structural intracranial lesions
- ✓ Partial epileptic seizures
- ✓ Chronic subdural haematoma
- ✓ Tumour
- ✓ Vascular malformation
- ✓ Multiple sclerosis
- ✓ Giant aneurysm
- ✓ Peripheral nerve or root lesion
- ✓ Labyrinthine disorders
- ✓ Metabolic
    - Hypoglycaemia
    - Hyperglycaemia
    - Hyponatremia
    - Hypercalcaemia
- ✓ Psychological

Symptoms of T I A

- ❖ Unilateral weakness or heaviness or clumsiness
- ❖ Unilateral sensory symptoms
- ❖ Transient monocular blindness
- ❖ Bilateral simultaneous blindness
- ❖ Homonymous hemianopia
- ❖ Dysarthria
- ❖ Dysphasia
- ❖ Unsteadiness/ataxia
- ❖ Diplopia
- ❖ Vertigo
- ❖ Dysphagia
- ❖ Bilateral motor loss
- ❖ Crossed sensory and motor loss

Clinical features of stroke

The diagnosis of stroke can be made without any difficulty, if there is a clear history of a focal brain dysfunction which was sudden in onset, or was first noticed when waking up in the morning, particularly in patients over 50 years of age , and has any of the vascular risk factors . There can be some progression of neurological deficit over the first few minutes or hours. But the deficit usually stabilizes by 12-24 hours and

recovery starts within a few days in most cases, if the patient survives . The severity of stroke ranges from a trivial deficit, which may recover in a day, through a persistent neurological deficit with or without any disability, to death within hours of onset. Now if the history is clear-cut, the chance of a CT scan or MRI brain showing anything other than an infarct or haemorrhage is under five per cent[40] [scan can even be normal if done early in the case of infarction or if the lesion is very small] .

If there is any doubt about the speed of development of a focal neurological deficit, then the diagnosis is rather more likely to be an intracranial space occupying lesion, which can either be a tumour or chronic subdural haematoma. Clinical clues to an intracranial tumour are recent headaches more severe in the early mornings, projectile vomiting, seizures, a worsening deficit over days or weeks and papilledema . It becomes more suggestive if there is any evidence of a primary tumour elsewhere . Now if the onset was clearly sudden, but without any obvious focal deficit, then brain imaging may be showing a thalamic or cerebellar lesion (infarct or haemorrhage).

. Clues to a chronic subdural haematoma are

- Recent head injury particularly in the previous few weeks
- More drowsiness, confusion and headache than that was anticipated from severity of the neurological deficit
- A fluctuating course
- Patient on anticoagulants.

Occasionally, head injury causing intracerebral haemorrhage may be missed if the patient cannot remember the injury itself and has no injuries over scalp . Ischaemic stroke shortly after an obvious head injury can be due to dissection of arteries in the neck.

Differential diagnoses for stroke are :

- Multiple sclerosis (young age)
- Post-seizure hemiparesis (history)
- Peripheral nerve or root lesion (clinical signs)
- Metabolic encephalopathy (global neurological features)
- Encephalitis (fever,diffusely abnormal eeg)
- Somatisation and hysteria (young age, absence of signs)
- intracranial abscess (fever, sinusitis, congenital heart lesion)[41]

Haemorrhagic strokes, causing a fall and so the subsequent head injury can be equally confusing as well to determine whether the stroke or the fall caused the ‘primary intracerebral haemorrhage' or 'subarachnoid haemorrhage' , as shown in the CT , particularly if the circumstances at the onset are unclear[42].

Now, If there are persisting residual signs from a previous stroke, and the patient falls ill for some reason or other such as an infection,or an epileptic attack , the old signs will now appear to worsen and may mimic a stroke recurrence .

Determining the exact site of the lesion in a case of stroke depends on skilful clinicoanatomical correlation[43]. There is a simple system, which usually do not require much neurological skill, which divides stroke patients generally into four main clinical categories:

- Total anterior circulation syndrome [TACS]
- Partial anterior circulation syndrome [PACS]
- Lacunar syndrome [LACS]
- Posterior circulation syndrome [POCS].

First, we have to put the patient in one of the above categories. This division depends entirely on the symptoms and signs, which are easily accessible to everyone, irrespective of the availability of any imaging modality or investigation technology.

Next, based on the CT scan of brain or perhaps MRI brain; the patients with primary intracerebral haemorrhage are separated from the rest. The remaining patients in whom the scan is either normal or may show an infarction in a relevant area, can be divided into:

1. Total anterior circulation infarct (TACI), which comes to about 15 per cent of the total in community-based studies
2. Partial anterior circulation infarct, 35 per cent (PACI)
3. Lacunar infarct, 25 per cent (LACI)
4. Posterior circulation infarct, 25 per cent (POCI)[44].

These categories of stroke may provide some vital prognostic information regarding survival, residual disability, recurrence, and also an indication of the cause of the stroke[45] as well.

Total anterior circulation syndrome [TACS]

Usually a bleed in one of the cerebral hemispheres, or an infarct which is large enough to affect the cortex of the brain, basal ganglia, as well as internal capsule, causes a characteristic clinical syndrome, which consists of contralateral hemiparesis, with or without any sensory deficit, which involves the whole or at least two of the three body parts [face, upper limb, lower limb]. Other features of TACS are a homonymous visual field defect,higher cerebral or 'cortical' dysfunction which includes dysphasia, neglect, visuospatial problems, etc.(depending on cerebral dominance).

Total anterior circulation infarcts (TACI) are usually due to sudden occlusion of the internal carotid artery (probably atherothrombotic), or due to embolic obstruction of the proximal middle cerebral artery originating from a proximal arterial or cardiac source[46].

Partial anterior circulation syndrome (PACS)

Sometimes a lobar haemorrhage, or a cortical infarct, may be causing a type of restricted clinical syndrome which consists of only few of the main components of typical TACS ie total anterior circulation syndrome.; or it can just be an isolated higher cortical dysfunction such as dysphasia. PACS may rarely present predominantly as a defective proprioception in one of the limbs; or a motor or sensory deficit that may be restricted to one or part of a body area[47]. If the 'cortical' signs are subtle like a dressing apraxia, neglect or dysphasia ,the patient may be misclassified as a 'lacunar' syndrome.

Partial anterior circulation infarcts (PACI) are caused usually by occlusion of a branch of middle cerebral artery. It can rarely be due to occlusion of trunk of the anterior cerebral artery. This occurs usually as a consequence of an embolism from the heart or any proximal vessel atherothrombosis, in the same way as that of total anterior circulation infarct. Anterior cerebral artery infarcts usually causes contralateral weakness, predominantly of the lower limb . There can be some cotical

sensory loss as well . If in the dominant hemisphere there can be aphasia also .

Lacunar syndrome (LACS)

Lacunar syndromes are due to small, deep lesions involving the motor and/or the sensory pathways .This can be in the corona radiata, thalamus, internal capsule, cerebral peduncle, and the pons[48] .

There are mainly 4 lacunar syndromes which can be most reliably defined if the patients are being examined at the time of their maximal deficit and there has been no history of previous stroke .

- pure motor stroke
- pure sensory stroke
- sensorimotor stroke
- ataxic hemiparesis

Posterior circulation syndrome [POCS]

Any brainstem, cerebellar, thalamic, or occipital lobe signs usually indicate an infarction in the distribution of the vertebrobasilar circulation[49] (i.e. posterior circulation), or a localized haemorrhage. A combination of brainstem signs as well as occipital lobe signs is highly suggestive of an infarction as part of thromboembolism within the basilar artery or posterior cerebral artery (PCA) territories. Sometimes, a proximal PCA occlusion causes temporal, thalamic as well as midbrain infarction to cause contralateral hemiparesis and hemisensory loss. There

may be marked cognitive deficit in the form of aphasia, as well as a homonymous hemianopia . This may be confused with occlusion of the middle cerebral artery or any of its branches[50] , and is referred to as 'walking total anterior circulation syndrome '. This occurs because, though it fulfills the definition of a total anterior circulation syndrome [TACS], the motor loss is usually mild and the patient may be able to walk . There are heterogenous causes for infarction in the vertebrobasilar territory the most common being embolic phenomenon.

Investigations in a case of stroke

- Complete blood count
- ESR
- Serum Electrolytes
- Blood Urea
- Blood glucose
- Lipid profile
- Urine routine
- Electrocardiogram

C T scan of Brain.

There is no alternative to a CT scan of Brain , when it is utmost essential to rule out a PICH . This is preferably to be taken within hours of onset of stroke that is before any haematoma has vanished. In the case of an ischaemic stroke CT scan can be normal immediately after onset of stroke.

If the lesion is very small (ie less than about 0.5 cm in diameter), or if it is in the posterior fossa, the CT scan may remain normal.

In case of larger infarcts, a diffuse hypodense area begins to appear . This is due to increasing water content in the brain, that occurs within a few hours. This hypodensity may be accompanied by effacement of sulci which may be subtle , and also loss of differentiation of normal grey and white matter . The loss of insular ribbon, loss of outline of lentiform nucleus, and also compression of adjacent ventricle[51] are other findings that can be seen in CT scan of patient with acute infarct . But when the lesion is large, more obvious findings like brain shift, infarct swelling and herniation can be made out in the CT , may be a few days after onset. Additionally, CT scan will show haemorrhagic transformation of the infarct, which can be either asymptomatic or symptomatic . This tends to occur a few days after stroke onset particularly in larger infarcts, but it can also happen within hours of onset and the haemorrhagic area can very well look like a primary haemorrhage[52] .

It should be remembered that MRI scan of brain is more sensitive , but it is less specific than C T scan. In case of Primary intracerebral haemorrhage (PICH), it appears at once on CT, as a well demarcated hyperdense area, round or oval in shape. This may or may not rupture into the ventricles or on to the surface of brain parenchyma. Unlike ischaemic stroke in haemorrhage , lesions as small as even 0.5cm in diameter can be picked up in CT scan. In primary intracerebral haemorrhage due to amyloid angiopathy, mixed-densities, suggesting blood of different ages, is seen as a characteristic feature. A blood-fluid level is highly suggestive of a haemostatic defect[53] , due to any reason . The availability of MRI is less than that of CT scan , and patients may have to lie still for longer periods . This makes CT scan the preferred immediate imaging modality, for acute stroke, particularly since it displays haemorrhage more reliably[54] than CT. But it should be remembered that MRI is not necessarily superior to CT scan in detecting the earliest signs of any cerebral infarction[55] .

Cortisol

In humans, cortisol is the predominant corticosteroid that is secreted from the adrenal cortex. Cortisol is secreted according to a diurnal pattern in a healthy, unstressed person. This is under the influence of corticotrophin hormone, which is released from the anterior part of

pituitary gland. Corticotrophin, which in turn, is under the control of the hypothalamic corticotrophin – releasing hormone. Both these hormones are subject to a negative feedback influence by the cortisol itself.

In the circulation cortisol hormone is bound to corticosteroid binding globulin. Only about 10 percent is in the free state, which is the bioavailable form. There is an increase in cortisol production, with severe infections, any trauma, burns, acute illness, or surgeries. This increase can be as high as 6 times the normal, which is roughly proportional to the severity of the illness[56]. The diurnal variation in secretion of cortisol hormone is also lost in acute illness. These effects seen in any acute illness is due to the fact that there is reduction in negative feedback from cortisol[57], and there is increased production of corticotrophin - releasing hormone as well as corticotrophin . The stimulation of hypothalamic - pituitary - adrenal axis that occurs in acute illness causing increased corticotrophin is due to elevated levels of circulating cytokines[58] .

The adrenal response to exogenously administered corticotrophin is normally maintained even during an acute illness[59]. In addition, during an acute illness, the level of corticosteroid binding globulin in blood decreases rapidly[60]. This leads to increased availability of cortisol at the sites of inflammation, probably due to the cleavage of corticosteroid - binding globulin by the neutrophil elastate, which will result in liberation of cortisol[61].

In addition to having these systemic actions, inflammatory mediators can cause an increased affinity of glucocorticoid receptors for cortisol. So these variations that occur in serum cortisol level as well as in its action during an acute illness, appear to be an important adaptive mechanism. In certain conditions the normal corticosteroid response that occurs during severe illness may be impaired .These factors are any preexisting conditions that may affect the hypothalamo - pituitary - adrenal axis[62] . The secretion of corticotrophin releasing hormone and corticotrophin may be impaired by injuries to head, any central nervous system depressant drugs and pituitary infarction[63] . But corticosteroid insufficiency can be seen during the course of any acute severe illness.

A variety of mechanisms may impair adrenal cortisol synthesis. The major drugs that can inhibit the action of enzymes[64] involved in production of cortisol are the anaesthetic agent etomidate and the antifungal agent ketoconazole.

Adrenal failure can occur with haemorrhage into the adrenal gland which occurs in severely ill patients, particularly with septicaemia and coagulopathy. Adrenal failure can also occur when adrenal tissue has been destroyed by tumors or by infections . In patients with sepsis the high levels of inflammatory cytokines can directly inhibit the adrenal cortisol synthesis[65].

A complex defense reaction called the "alarm reaction" may be triggered by an ischaemic stroke. The stress caused by stroke gives rise to liberation of variety of mediators like catecholamines, dopamine and beta-hydroxylase in the blood as well as in cerebro-spinal fluid . It was found that patients with ischaemic stroke have increased levels of adrenaline, noradrenaline, and 3-metoxy,4-hydroxymandelic acid in urine, as well as increased cortisol levels in blood . Patients, with stroke have an increased concentration of glucose and its metabolites (pyruvate acid, lactic acid, acetylacetic acid) in blood and cerebro-spinal fluid..

In any acute severe illness, the synthesis of cortisol hormone increases whereas that of adrenal androgens and dehydroepiandrosterone decreases. Often, following stroke there occurs a time period which can be considered as a very stressful condition. Changes in cortisol secretion are one of the indicators of this stress reaction .

Normally the increased levels of glucocorticosteroid hormones , secreted from the adrenal cortex in the event of any stressful condition have negative effects on many organ systems and may even impair the immune system. It also impairs the myocardial function and has effects on the metabolism of carbohydrates, proteins and fats .

Various studies conducted In vitro and in vivo have clearly proved the neurotoxic effects of glucocorticosteroids, including potentiation of ischaemic injury to the neurons[66,67]. Experimentally the

hypoxic injury to neurons is exacerbated by high levels of glucocorticosteroids and attenuated after adrenalectomy[68,69].

It has been found that prolonged persistent exposure to glucocorticosteroids may influence the cognition and mood[70] of an individual. This is because hippocampal formation which is inevitable in maintaining mood as well as cognition has a high density of glucocorticosteroid receptors[71]. However, adequate glucocorticosteroid levels in the circulation is essential for maintaining body homeostasis[72] as adrenalectomy itself can cause neuronal injury .

Acute cerebrovascular accident is associated with an heightened activity in the hypothalamo-pituitary-adrenal axis, which results in increased circulating serum cortisol levels[73] . Various previous researches have shown that increased serum cortisol levels after an acute cerebrovascular accident is associated with cognitive dysfunction[74]. It also indicates severity of stroke and may predict functional outcome[75,76].The development of depression[77] later also correlates with serum cortisol level . To the contrary, low levels of serum cortisol has been associated with adverse outcome in burns and septicemia[78,79,80], which shows the importance of glucocorticosteroids in the maintenance of vital functions.

It is observed that during the early days following an acute stroke, there is an initial increase in corticotrophin and cortisol levels ,but subsequently,

rapid decrease of corticotrophin occurs with a persisting increased cortisol levels. This dissociation between corticotrophin and cortisol is due to cortisol-induced supression of corticotrophin release combined with an increased secretion of cortisol at the level of adrenal glands[74].

Increased production of cytokines (release of interleukins-1,6 and tumour necrosis factor alpha) in stroke patients, which can act on several levels at the HPA axis[80,81] may be parly responsible for the observed dissociation between cortisol and corticotrophin levels. The elevated cortisol levels may induce cognitive dysfunction[82] and experimentally it has been proved that glucocorticosteroids in connection with ischaemia can cause a toxic effect on neurons, especially that of the hippocampus[83] . The hippocampal pyramidal neuron degeneration thus induced may lead to hypercortisolism. This is because hippocampus is believed to be important for the feedback inhibition of the HPA axis[84] by the cortisol ,and hippocampal stimulation during surgery is known to inhibit the HPA axis in man .

It has been shown that administration of even minor doses of exogenous cortisol can cause a impaired cognitive performance. This suggests that disorientation or impaired cognition may be an important contributor to, and may predict the functional outcome in acute stroke[85].

MATERIALS AND METHODS USED

Patients

This study included a total number of 65 patients who were admitted with acute stroke within a period of 24 hrs of onset . Informed consent was obtained . The patients were recruited from medical wards and IMCU of the medical college hospital . Out of the total 65 patients, 15 patients were excluded as per the exclusion criteria.

The remaining 50 patients were selected for the study.

Exclusion criteria used

- Age <18
- Liver disease
- Pregnancy
- recurrent stroke
- Patients who are taking following drugs
    - Phenytoin
    - Steroids
    - Rifampicin
    - Ketaconazole

METHODOLOGY

At the time of admission in the hospital the pulse rate, systolic and diastolic blood pressure, and Scandinavian Stroke Scale (SSS) were recorded in all the patients. A diagnosis of cerebral infarction or an intracerebral haemorrhage was based on clinical findings as well as history at the time of admission and with the help of

CT-scan in all these patients. Blood samples were taken for total count, blood sugar values, and serum cortisol levels.

Barthel index and Modified Rankin score are calculated at discharge and then monthly till 3 months from onset of stroke. Single-measurement of serum cortisol at admission was chosen as, earlier studies have shown that the circadian rhythm of cortisol secretion is lost in acute stroke.

SCANDINAVIAN STROKE SCALE

[Scandinavian Study Group on Stroke of1985]

CONSCIOUSNESS:

- Full conscious level – 6
- In somnolent state, can be awaked -4
- Responds to verbal commands, but not having full conscious level - 2
- coma - 0

ORIENTATION:

- Oriented for time, place and person – 6
- Any two of above three – 4
- Any one of above three -2
- Complete disorientation – 0

SPEECH:

- Not having any aphasia – 10
- Decreased comprehension or expression - 6
- More than yes/no ; but no longer sentences – 3
- Only yes/no or less – 0

EYE MOVEMENT:

- Gaze palsy absent – 4
- Gaze palsy present – 2
- Forced lateral gaze present - 0

FACIAL PALSY:

- None – 2
- Present – 0

GAIT:

- Walks > 5 m without aids – 12
- Can walk with aid – 9
- Can walk with help of a person – 6
- Can walk without any support – 3
- Bedridden or wheelchair bound – 0

ARM, MOTOR POWER (Assessed on affected side only):

- Can raise arm with normal power – 6
- Raises arm with reduced power – 5
- Raises arm with flexion in elbow – 4
- Can move, but not possible against gravity – 2
- paralysis – 0

HAND, MOTOR POWER (Assessed on affected side only):

- Normal power – 6
- Reduced power in full range - 4
- Some movement, but fingertips cannot reach palm – 2
- Paralysis – 0

LEG, MOTOR POWER (Assessed on affected side only):

- Normal power – 6
- Raises straight leg with reduced power – 5
- Raises leg with flexion of knee – 4
- Can move, but not against gravity – 2
- Paralysis – 0

FOOT PARESIS:

- None – 2
- Present - 0

THE BARTHEL INDEX

FEEDING

- Not able - 0
- Needs help / requires modified diet - 5
- Independent - 10

BATHING

- Dependent – 0
- Independent - 5

GROOMING

- Needs help – 0
- Independent - 5

DRESSING

- Dependent – 0
- Needs some help – 5
- Independent - 10

BOWELS

- Incontinent / needs enemas - 0
- Occasional accident – 5
- Continent - 10

BLADDER

- Incontinent / catheterized – 0
- Occasional accident – 5
- Continent – 10

TOILET USE

- Dependent – 0
- Needs some help – 5
- Independent - 10

TRANSFERS (BED TO CHAIR AND BACK)

- Not able to do – 0
- Major help by one or two people - 5
- Minor help (verbally or physically) – 10
- Independent - 15

MOBILITY (ON LEVEL SURFACES)

- Immobile or less than 50 yards – 0
- Wheelchair for more than 50 yards – 5
- Walks with help of a person – 10
- Independent (may use walking aid) - 15

STAIRS

- Not possible – 0
- Needs help (verbally or physically) – 5
- Independent - 10

MODIFIED RANKIN SCORE

- No symptoms - 0
- No significant disability ;able to carry out usual duties-1
- Slight disability; not able to carry out all previously done activities, but able to look own affairs -2
- Moderate disability; but able to walk without any assistance -3
- Moderately severe disability; not able to walk and take care of self without assistance - 4
- Severe disability; bedridden and incontinent - 5
- Dead - 6

SERUM CORTISOL

Serum cortisol was estimated by the competitive immunoenzymatic colorimetric method. Cortisol (antigen) present in the serum sample competes with horse radish peroxidase-cortisol complex (enzyme labeled antigen) for binding on to the anti-cortisol antibodies on the microplates (solid phase) which is limited in number. After incubation, separation of bound and free forms is done by a simple washing of solid phase . Now the enzyme substrate (H_2O_2) and the Tetramethyl benzidine (TMB) substrates are added. TMB acts as an hydrogen donor for the enzymatic reduction of H_2O_2 to water . The

resulting TMB diimine gives a blue colour . After appropriate time is elapsed for maximal colour development, the absorbance is determined. The colour intensity observed is inversely related to the cortisol concentration in the sample. The analyzing laboratories were not given clinical information about patients.

Serum cortisol level is now compared with SSS (scandinavian stroke scale) score and any correlation with stroke severity is identified. We also check any correlation between cortisol level and stroke severity as given by Scandinavian Stroke Scale with other clinical and biochemical parameters like blood pressure , total count ,blood glucose etc.

As diurnal variation of cortisol level is lost in stroke , only one value of cortisol at time of admission is needed for the study. At the end of 3 months clinical outcome of stroke as defined by Barthel Index and Modified Rankin Score is compared with admission day serum cortisol level.

STATISTICAL ANALYSIS

The information gathered about all the selected cases were recorded in a master chart. Data was analysed with the help of a computer by using SPSS software and Sigma Stat 3.5 version (2012). Using the software range, frequencies, percentage, mean, standard deviation and ‘p’ value were calculated through One way ANOVA, Chi square, Pearson and Spearman Correlation test . **P value of < 0.05** was taken as significant. (95% confidence interval) .

RESULTS AND OBSERVATIONS

Out of the total 50 patients included in the study 39 were male patients and 11 female patients . All 50 patients were admitted within first 24 hours of onset of stroke .

SEX DISTRIBUTION

Sex	No.of cases	Percentage
Male	39	78
Female	11	22

The mean age of presentation is 62 years. Minimum age of patient that was registered in the study was 40 years and maximum age 90 years . There were 24 patients below the age of 60 years and 26 patients aged above 60 years.

Age in years	Number of patients
< 60	24
> 60	26

Out of the total , 35 patients were known hypertensives. This comes to about 70% .

HTN	No.of cases	Percentage
Yes	35	70%
No	15	30%

42 % of stroke patients were known diabetics ,ie 21 cases out of the total 50

T2DM	No.of cases	Percentage
Yes	21	42%
No	29	58%

17 patients (34 %) had both diabetes and hypertension., and 11 patients (22%) were free of both diabetes and hypertension .

	T2DM Yes(21)	T2DM No(29)
HTN Yes (35)	17	18
HTN No (15)	4	11

22 patients (44%) admitted with stroke were smokers and 16 patients (32%) were alcoholics.

	No.of cases	**Percentage**
Smokers	22	44 %
Non Smokers	28	56%

	No.of cases	**Percentage**
Alcoholics	16	32 %
Non Alcoholics	34	68%

11 patients out of the total 50 were both alcoholics as well as smokers, which comes to about 22% . About 23 patients (46%) were non smokers as well as non alcoholics. Alcoholism and smoking were exclusively seen in male patients.

	Smoker	**Non smoker**
Alcoholics (16)	11	5
Non Alcoholics (34)	11	23

The patient characteristics can be summarised as

Patient characteristics (N=50)	Percentage or average
Age	62 years
Male sex	78%
Hypertensive patients	70%
Diabetic patients	42%
Smokers	44%
Alcoholics	32%

Of the total 50 patients enrolled for the study, 16 (32%) patients were having haemorrhagic stroke , and the remaining 34 (68%) patients were suffering from ischaemic strokes. It was noted that the most common site for ischaemic stroke was Middle cerebral artery territory. The average systolic blood pressure recorded in the patients on admission was about 162 mm Hg, with a standard deviation of 21.75 ,and all the patients were having a systolic blood pressure more than 130 mm Hg .

The average diastolic blood pressure recorded was 98 mm Hg on admission, with a standard deviation of 8.73, and no patient was having a diastolic blood pressure less than 80 mmHg. The highest diastolic blood pressure recorded was 120 mm Hg.

The investigations revealed a total WBC count of about 10214 cells/cu.mm as an average , with a standard deviation of 3320 cells. Blood sugar estimation showed an average random blood sugar of 134 mg/dL, with a standard deviation of 29 mg/dL.

Serum cortisol measured at the time of admission ranged between 2.36 mcg/dl to 42.3 mcg/dL. [reference range 3.09 – 16.66 mcg/dl] Serum cortisol showed a mean of about 18.43 mcg/dl, with a standard deviation of about 9.93 mcg/dL. The mean cortisol value was more in male patients and in patients aged more than 60 yrs.

Age in years	**Cortisol Mean value**
< 60	17.7
> 60	19.1

Sex	**Cortisol Mean value**
Male	19.11
Female	16.05

It was also observed that mean cortisol value was significantly higher in patients with haemorrhage compared to ischaemic stroke patients.

	No.of cases	Cortisol Mean
Haemorrhage	16	23.18
Infarct	34	16.2

Patient profile on admission

Patient indicators	Mean	Standard deviation
SBP	162 mm Hg	21.75
DBP	98 mm Hg	8.73
Total Count	10214cells/cu.mm	3320
Blood Sugar	134 mg/dl	29mg/dl
Serum Cortisol	18.43 mcg/dl	9.93 mcg/dl

The Scandinavian stroke scale assessment , which is a measure of severity of stroke ,ranged from 4 to 50 in our patients for a total of 60, at the time of admission.

The mean Scandinavian stroke scale(SSS) score is about 27.7 with standard deviation of about 12.03.

	Mean	Standard deviation
Scandinavian stroke scale (At admission)	27.7	12.03

The Barthel Index, (at discharge) which is an index of functional outcome ranged from 5 to 55 out of a total of 100 . The mean being 31 with a standard deviation of 12.49. The Barthel Index after a period of 3 months ranged from 0 to 95 , with a mean of 61.90 and standard deviation of 23.03

	Mean	**Standard deviation**
Barthel Index (at discharge)	31	12.49
Barthel Index (at end of 3 months)	61.90	23.03

At the time of discharge , the Modified Rankin Score, which is also a measure of functional outcome of stroke patients ranged from 3 to 6 , out of a total of 6 . The average Modified Rankin Score was 3.98 with a standard deviation of 0.714.

At the end of 3 months the Modified Rankin Score ranged from 1 to 6 , with a mean of 2.40 and a standard deviation of 1.16

	Mean	Standard deviation
Modified Rankin Score (at discharge)	3.98	0.714
Modified Rankin Score (at end of 3 months)	2.40	1.16

The correlation between serum cortisol and scandinavian stroke scale (SSS) score was analysed , and was found to be statistically significant with a P value of < 0.001.

Similar significant correlation (P value < 0.001) was found between serum cortisol and indices of functional outcome like Barthel index (B.I) and Modified Rankin Score (MRS) .

At the end of 3 months the functional outcome of the patients as given by MRS showed high correlation with the admission day cortisol level . the correlation coefficient being 0.819

The relationship between serum cortisol and various other parameters like systolic blood pressure[SBP], diastolic blood pressure[DBP] , total count and admission blood sugar level were also analyzed , which was found to be statistically significant . Similar relationship existed between SSS score and these parameters.

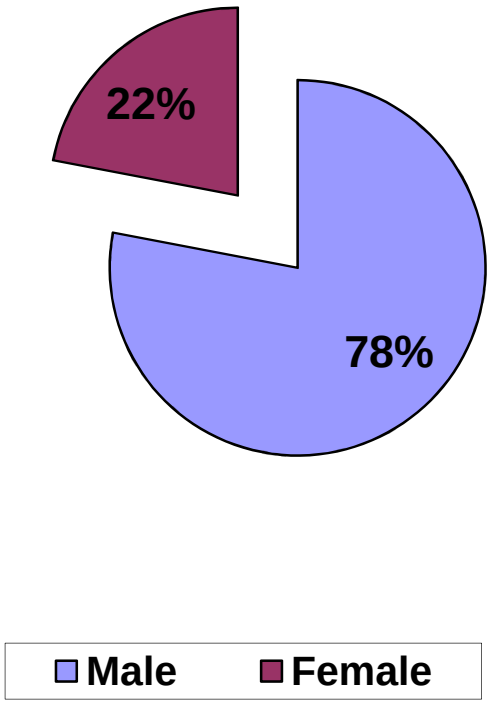
The levels of correlation between serum cotisol and these parameters were computed.

LEVELS OF CORRELATION WITH SERUM CORTISOL:

Factor	**Correlation coefficient**
Systolic blood pressure[SBP]	0.602
Diastolic blood pressure[DBP]	0.337
Total count	0.698
admission blood sugar	0.748

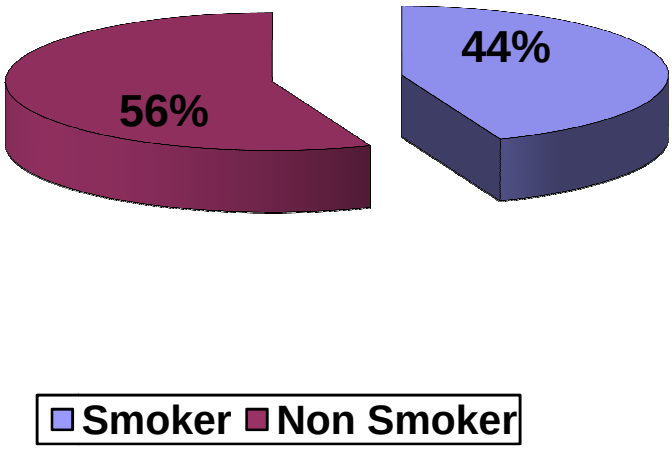
The highest magnitude of correlation was obtained for the admission time random blood glucose levels, and the lowest was obtained for diastolic blood pressure as depicted above.

SEX DISTRIBUTION



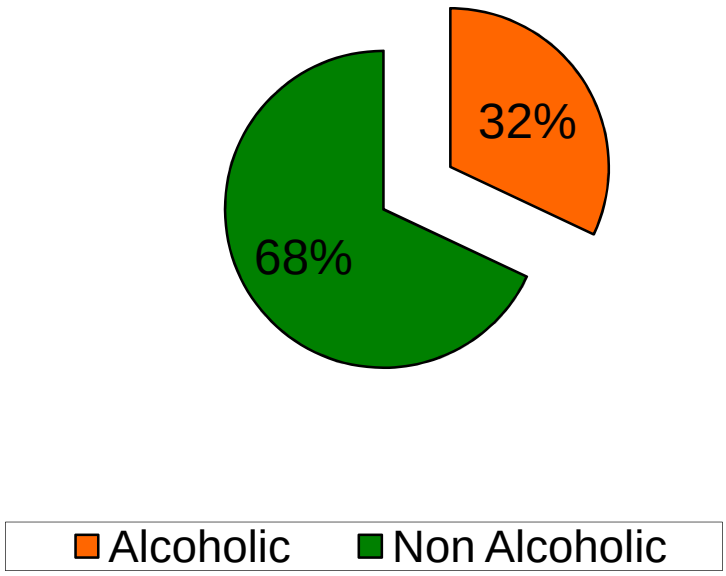
This graph shows the male and female distribution among stroke patients .39 Patients out of the total 50 were males which comes to about 78 % . This goes with the fact that cigarette smoking and alcoholism which are risk factors for stroke were exclusively seen in males.

SMOKING IN STROKE PATIENTS



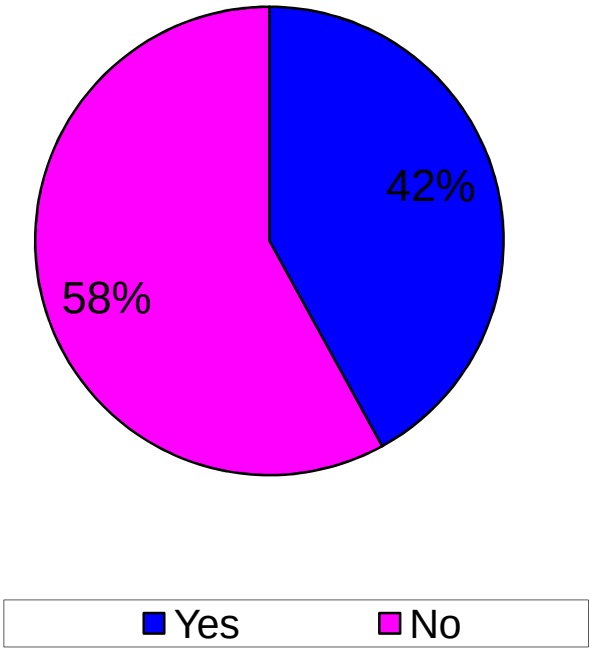
This graph depicts the burden of smoking in the study group . 22 of the total 50 patients admitted with stroke were chronic smokers .This also includes ex- smokers who have already quit smoking . This comes to an alarming 44% of the total stroke patients. Smoking was exclusively seen in male patients.

ALCOHOLISM IN STROKE PATIENTS



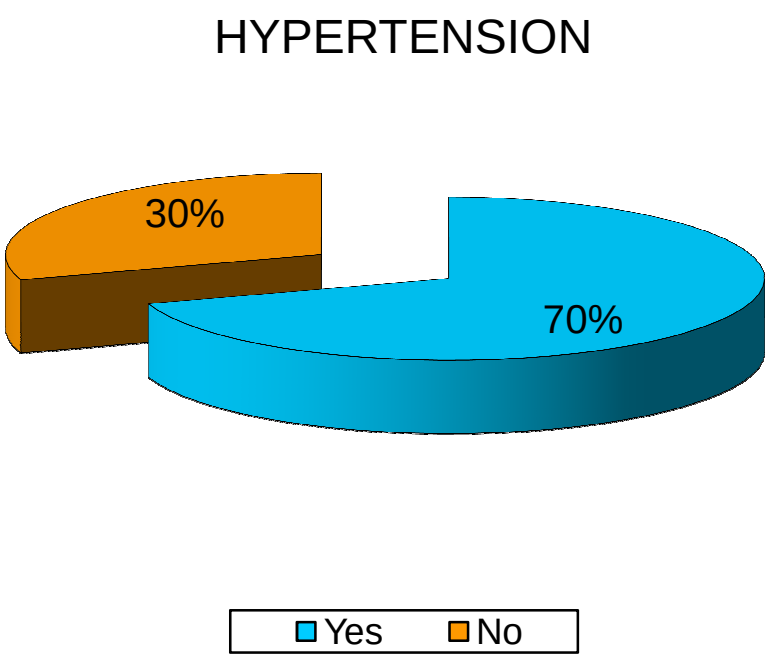
16 of the total 50 patients admitted with stroke were chronic alcoholics . This comes to about 32 % of the total patients .Alcoholism was seen exclisively in male patients .

DIABETIC BURDEN AMONG STROKE PATIENTS

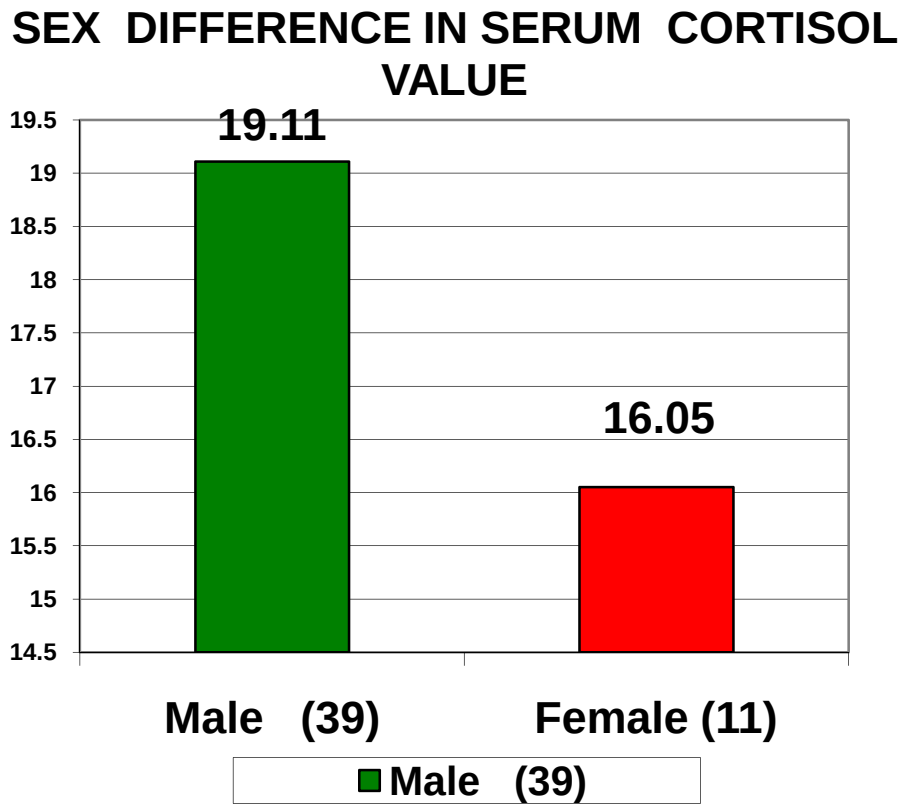


21 patients of the total 50 were diabetics . This comes to about 42% of the total .This included newly detected as well as known diabetic patients .

HYPERTENSION AS A RISK FACTOR FOR STROKE

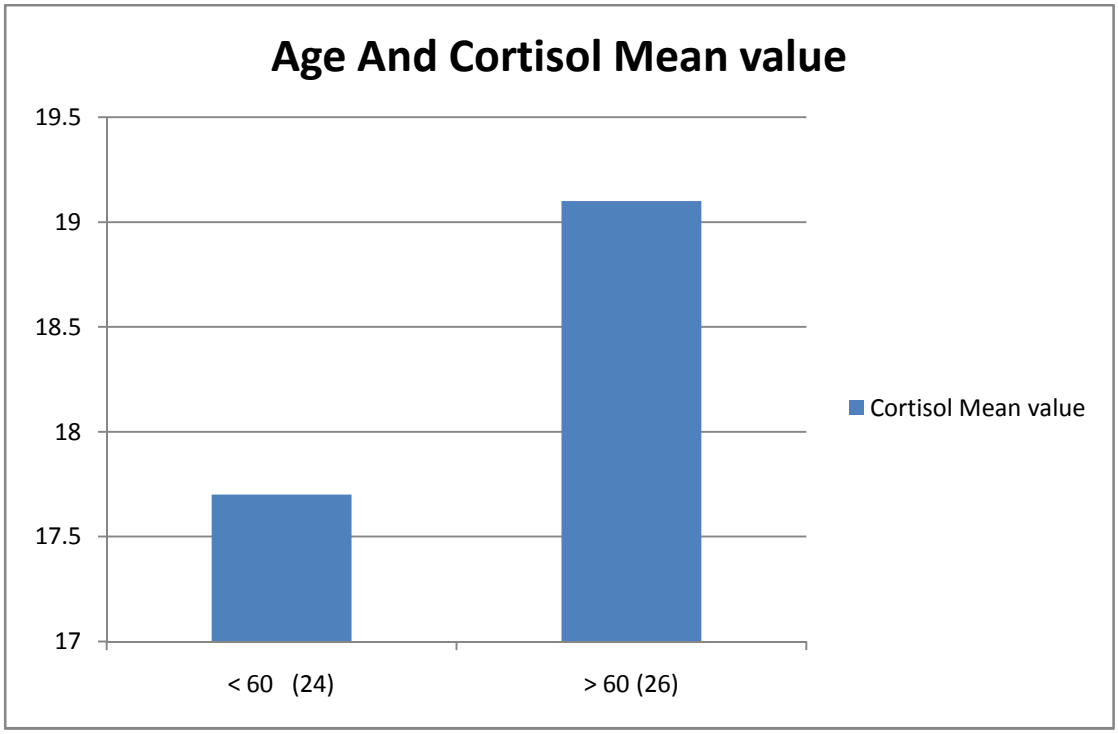


35 patients admitted with stroke were hypertensives . This comes to 70% of the total. Hypertension is the most common risk factor observed in the patients. Both newly detected as well as known hypertensives were included .

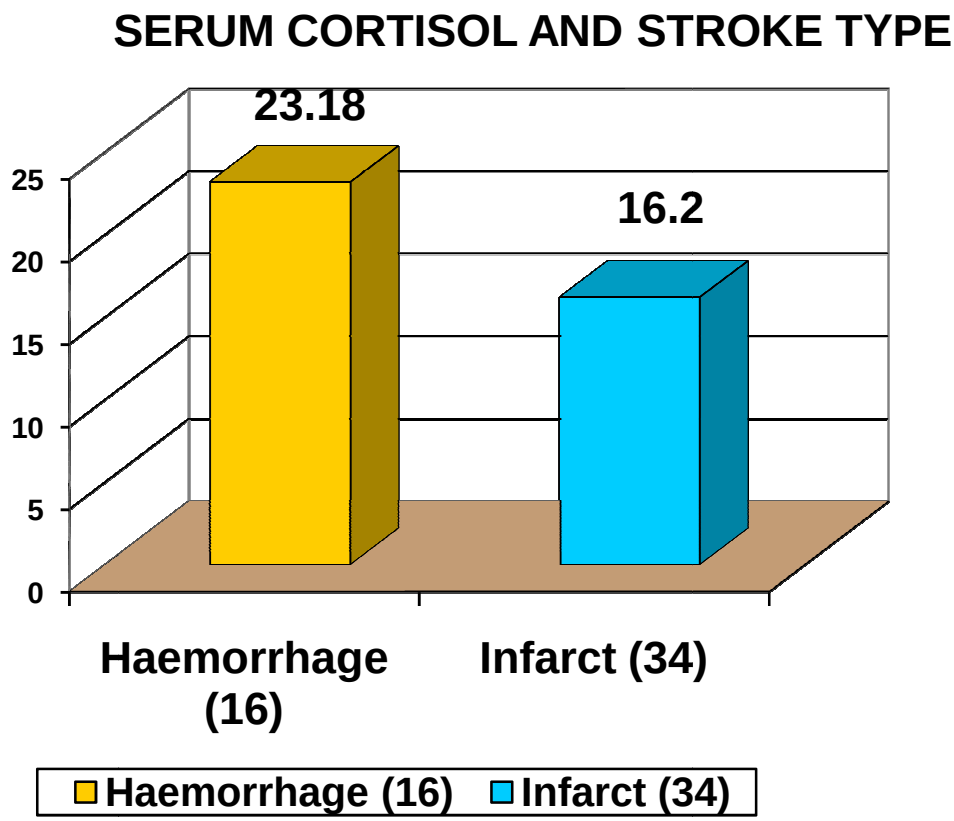


In the study it was found that the average serum cortisol values were higher in male patients . The average serum cortisol value in males was 19.11 mcg/dl , whereas it is 16.05 mcg/dl in females .

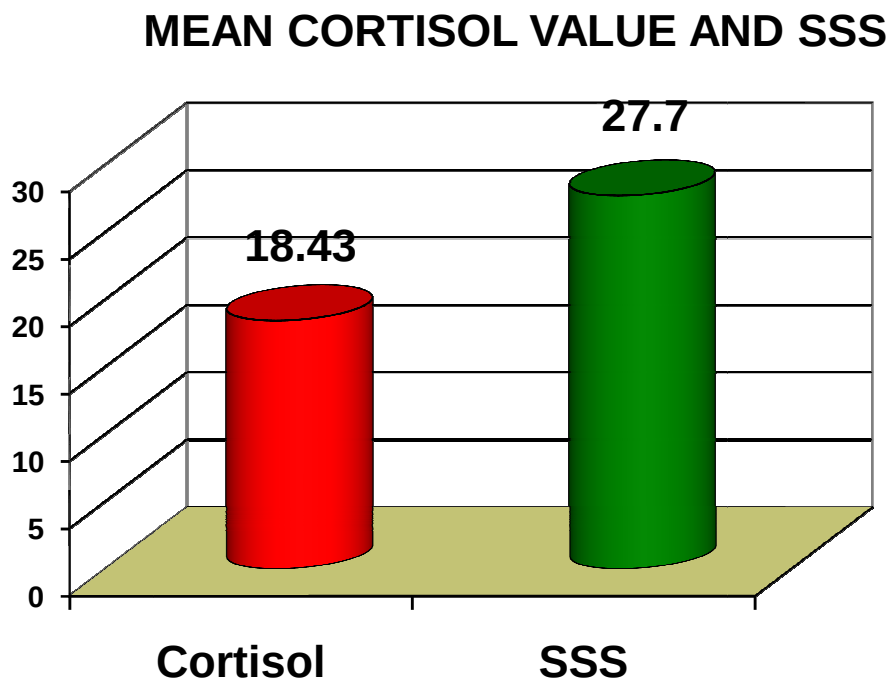
IMPACT OF AGE ON CORTISOL VALUE



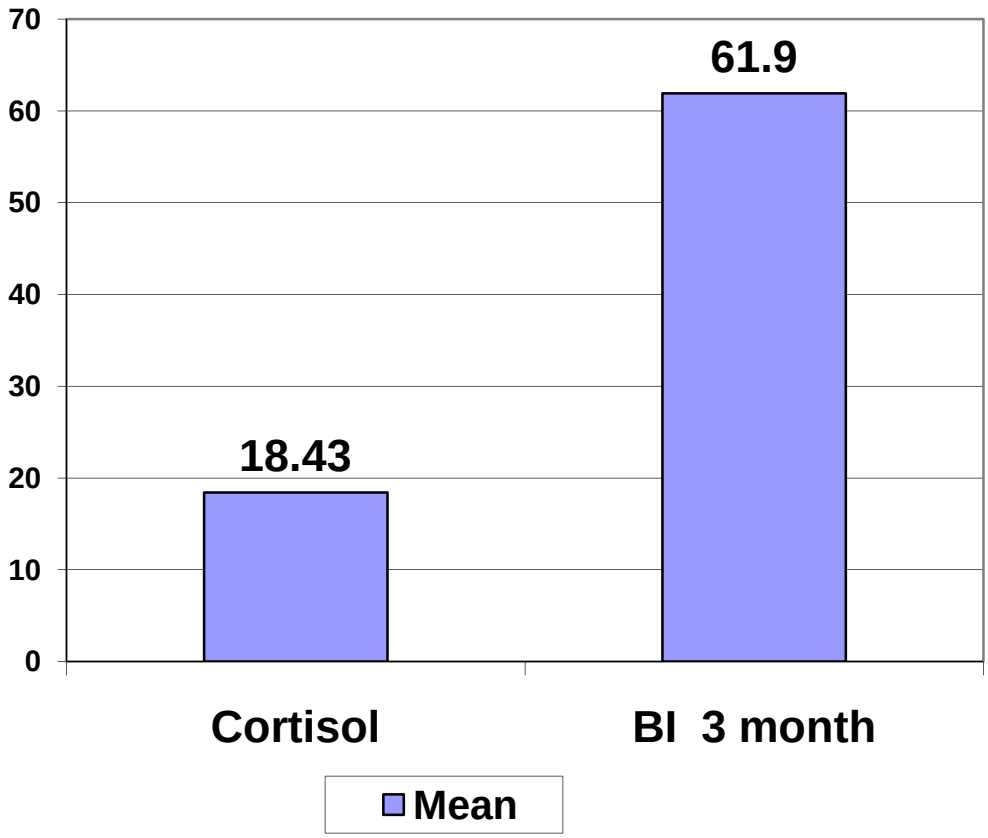
It was also found that mean cortisol value was higher in patients aged more than 60 years . There were 24 patients with age less than 60 yrs and 26 patients were above 60 years out of the total 50 . The average cortisol value in the age group below 60 years was 17.7 mcg/dl and in the age group above 60 years was 19.1 mcg/dl .



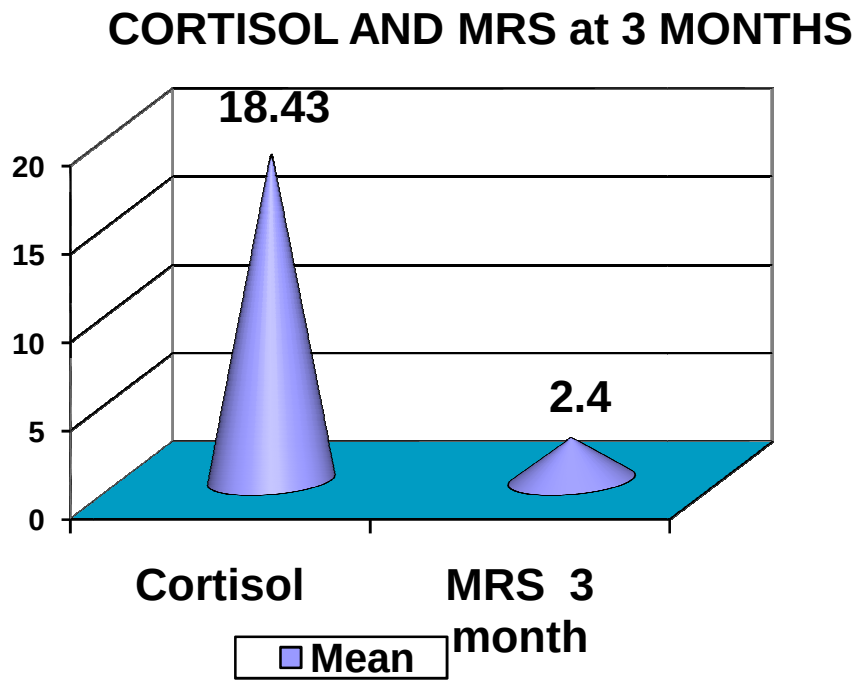
Out of the 50 patients 34 patients were admitted with ischaemic stroke. It was observed that the average serum cortisol values were higher in haemorrhagic stroke .



At admission the mean serum cortisol value was 18.43 mcg/dl , and the mean SSS score which indicates the severity of stroke was 27.7 . SSS ranges from 0 to 60 . The reference range for serum cortisl is between 3.09 mcg/dl to 16.66 mcg/dl .

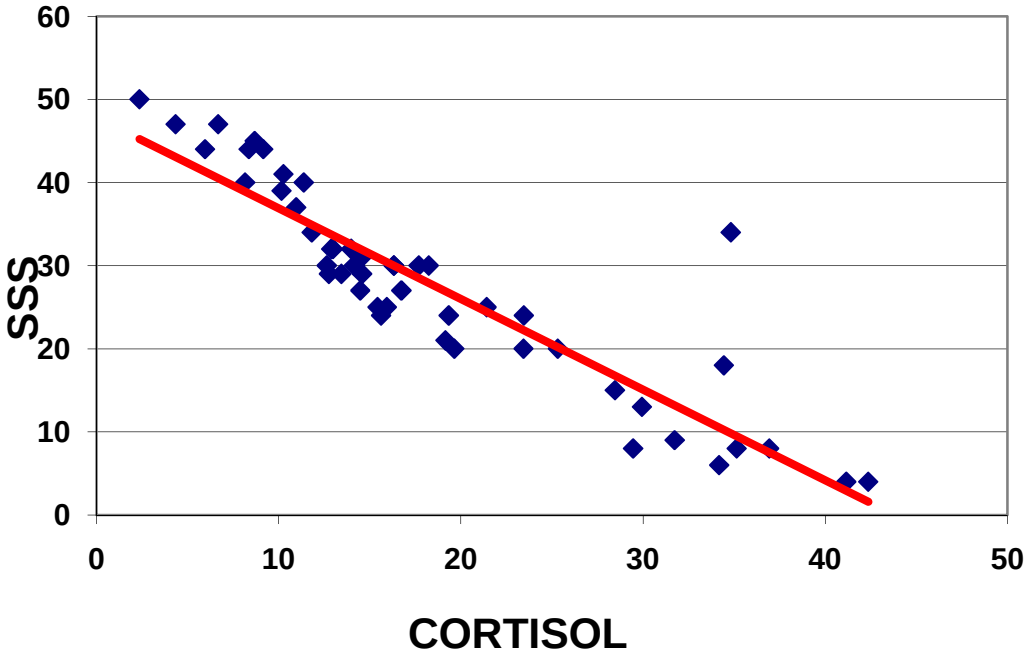


The Barthel Index (BI) after a period of 3 months , which is a measure of functional outcome in stroke patients ranged from 0 to 95 out of a score of 100.



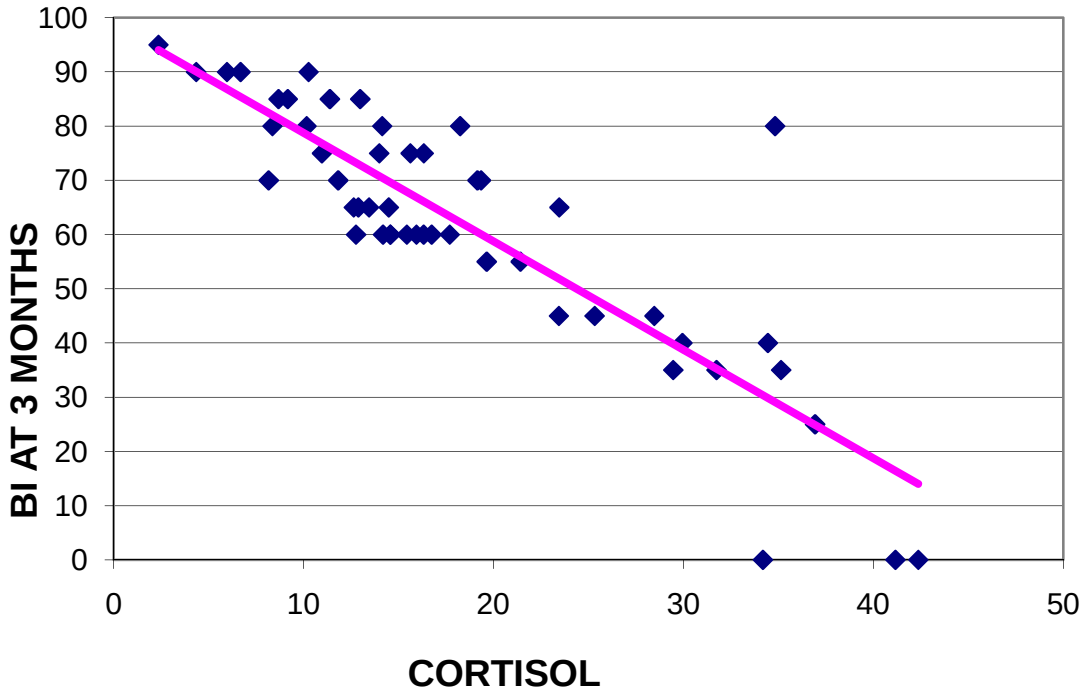
The Modified Rankin Score (MRS) is a measure of functional outcome . The MRS at the end of 3 months ranged from 1 to 6 with a mean of 2.4.

RELATION OF SERUM CORTISOL AND SSS



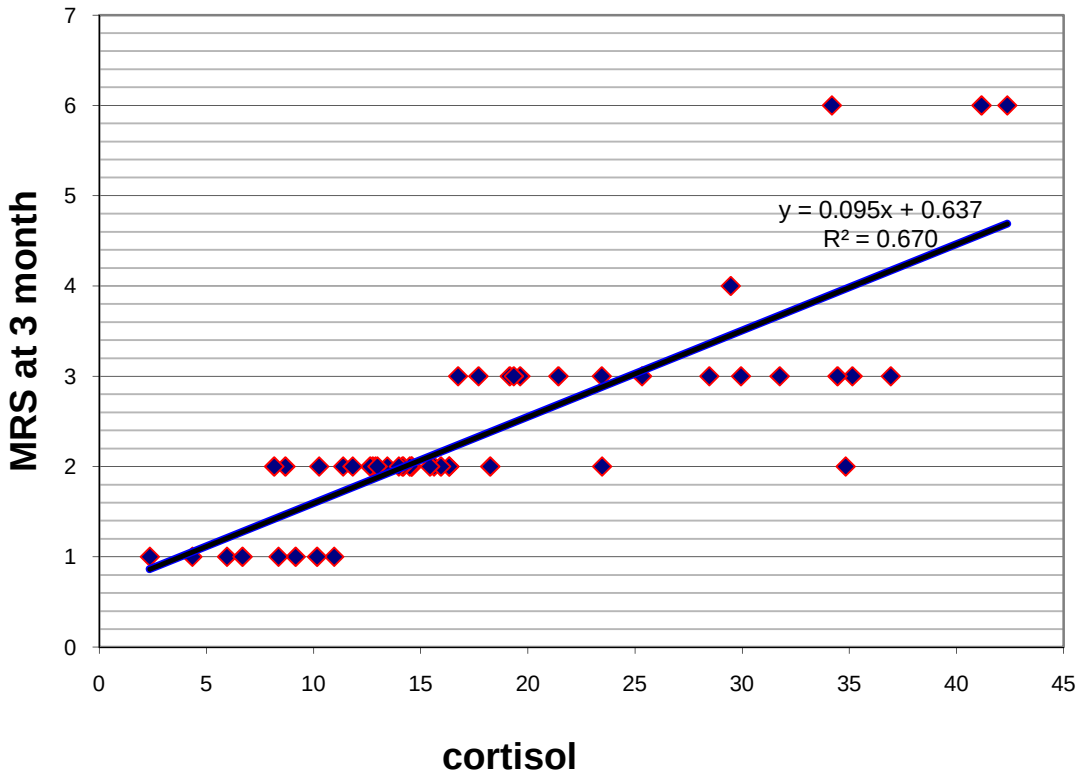
This graph shows that as serum cortisol increase the SSS score decreases and hence shows more severe stroke. Thus there is an inverse correlation between serum cortisol value and SSS score .

CORRELATION BETWEEN SERUM CORTISOL AND BARTHEL INDEX



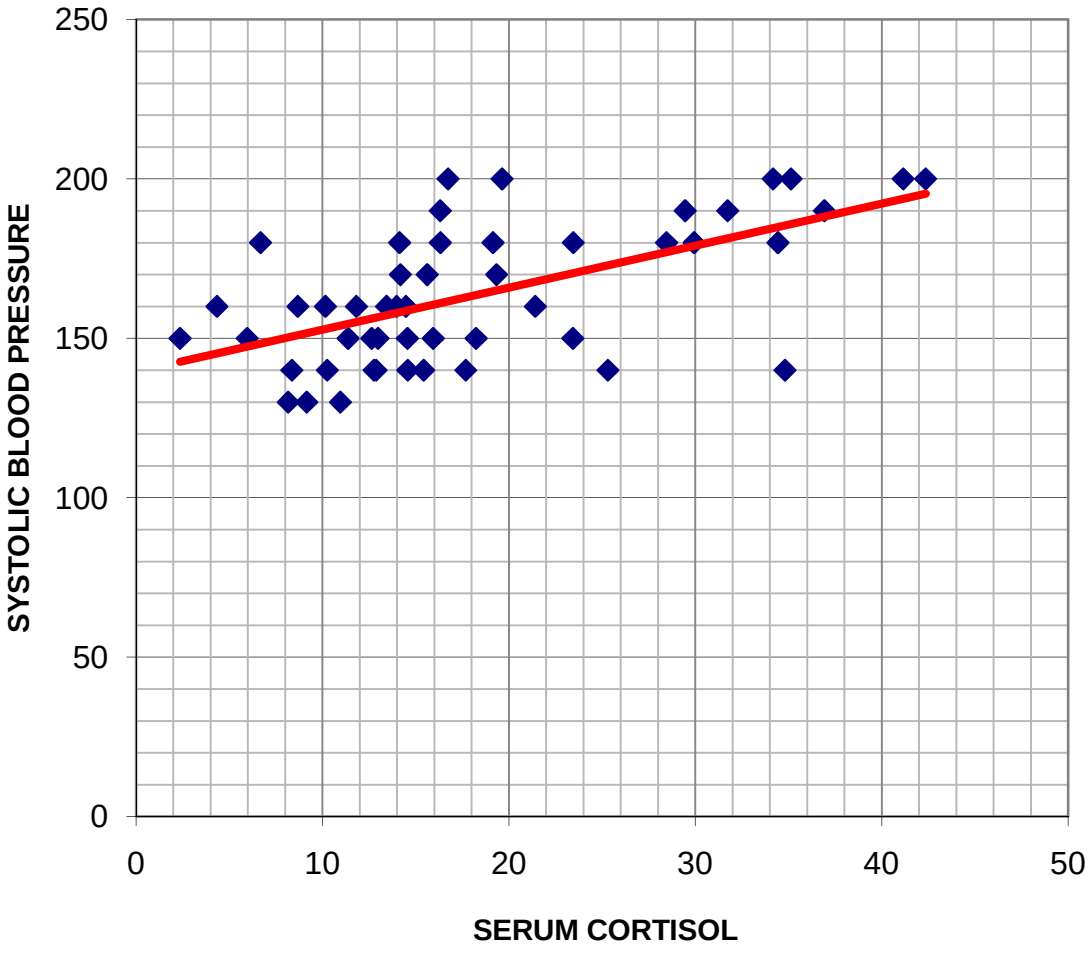
The Barthel index is a measure of functional outcome . This graph shows that as cortisol value increases the Barthel index decreases indicating poor functional outcome. So serum cortisol is inversely related to the Barthel Index .

CORRELATION BETWEEN SERUM CORTISOL AND MODIFIED RANKIN SCORE



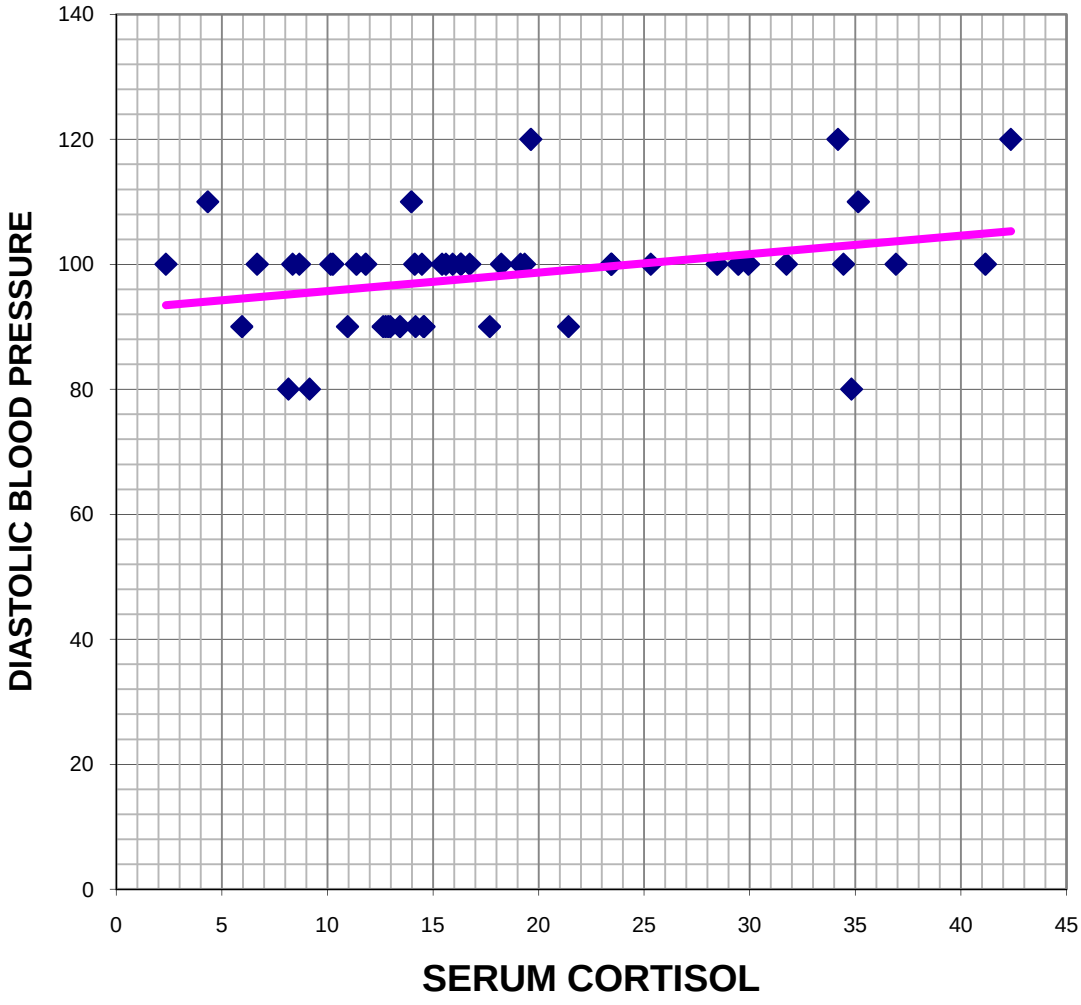
Modified Rankin Score (MRS) indicates functional outcome in stroke patients. This graph shows that as cortisol value increases in stroke patients , the MRS also increases indicating poor functional outcome . High correlation was observed between serum cortisol and MRS at the end of three months, correlation coefficient being 0.819.

CORRELATION BETWEEN SERUM CORTISOL AND SYSTOLIC BLOOD PRESSURE



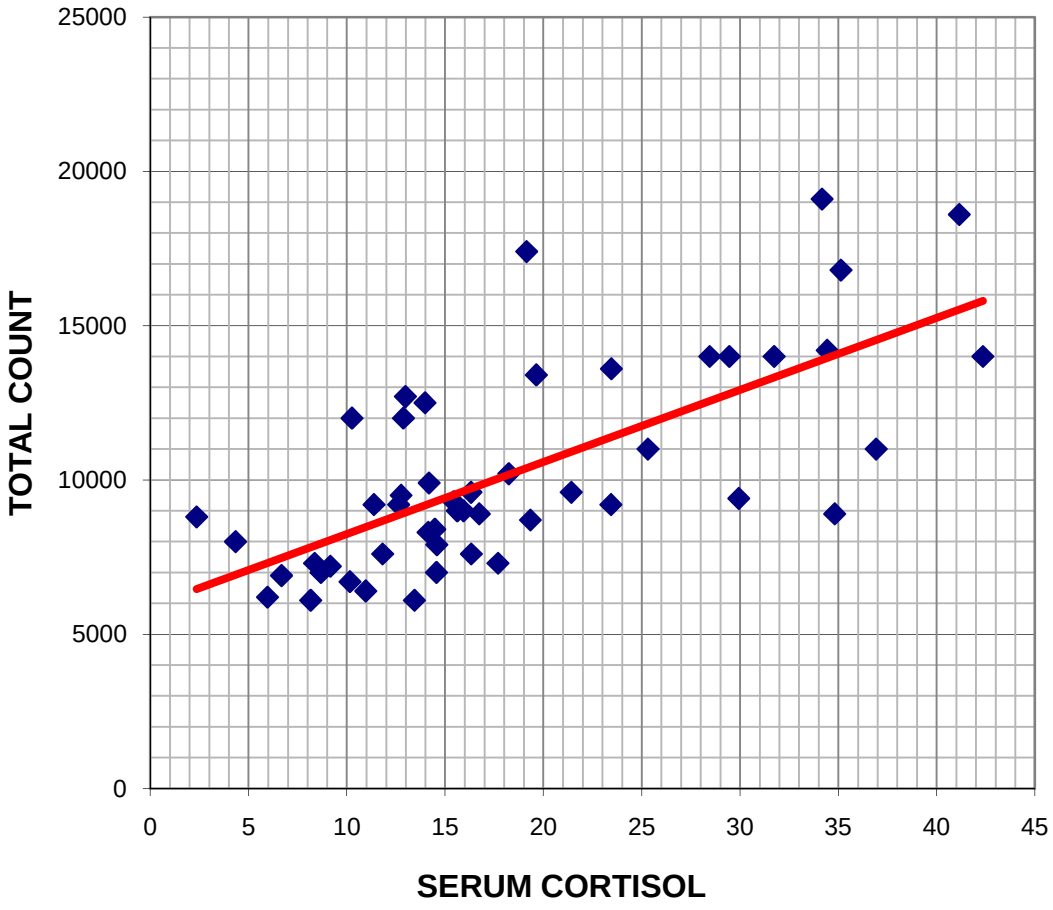
Systolic blood pressure shows a positive correlation with serum cortisol . Patients with elevated systolic blood pressure had high serum cortisol levels and poor prognosis . The correlation coefficient for systolic blood pressure and serum cortisol is 0.602.

CORRELATION BETWEEN SERUM CORTISOL AND DIASTOLIC BLOOD PRESSURE



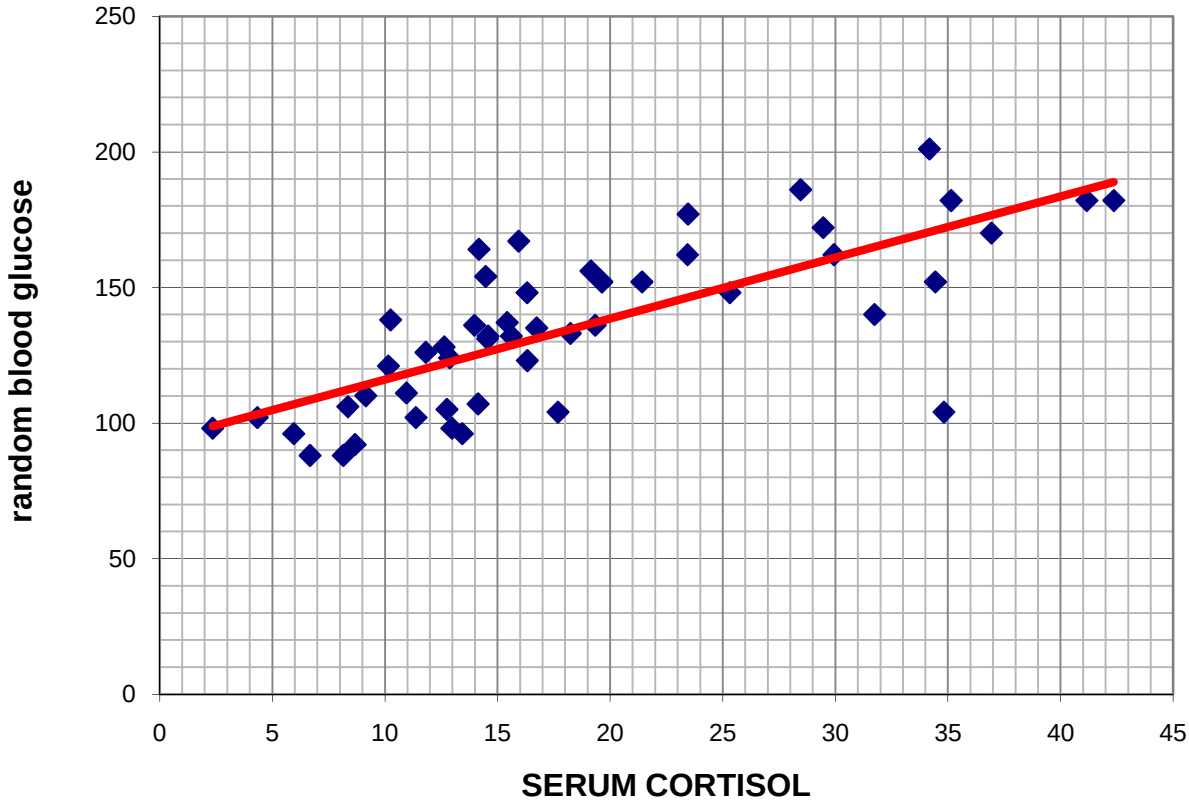
This graph shows a positive correlation between serum cortisol and diastolic blood pressure . We can see that as serum cortisol increases diastolic blood pressure increases but to a lesser degree as compared to systolic blood pressure . The correlation coefficient for diastolic blood pressure and serum cortisol is 0.337.

CORRELATION BETWEEN SERUM CORTISOL AND TOTAL COUNT



Serum cortisol shows a positive correlation with total count . The correlation coefficient is 0.698.

CORRELATION BETWEEN SERUM CORTISOL AND RANDOM BLOOD GLUCOSE



This graph shows a positive correlation between serum cortisol and random blood glucose at the time of admission , in stroke patients . Blood glucose shows the highest level of correlation with serum cortisol .

DISCUSSION

This study was conducted on Indian population involving 50 patients admitted with cerebrovascular accident within a period of 24 hours of onset . Here we evaluated the relationship between admission day serum cortisol level and stroke severity as determined by Scandinavian stroke scale (SSS) score. The study showed a statistically significant correlation between serum cortisol and stroke severity.

Earlier studies like that conducted by Department of Neurology, University of Copenhagen , have shown that elevated serum cortisol is an indirect indicator of stroke severity.

Christensen H, Boysen G, et al.(2004) did a study in acute stroke on 172 patients and showed Serum-cortisol reflects severity and mortality[86] . It was also shown that serum cortisol correlated well with scandinavian stroke scale , pulse rate and body temperature.

This was evident from our study that showed a statistically significant correlation between serum cortisol and SSS scores($P<0.001$). SSS score is inversely related to the stroke severity, ie lower the score, higher the severity . In our study it was observed that patients who had high cortisol values on admission have a lower SSS score and hence more severe stroke, and this observation was statistically significant .

We also tried to correlate between serum cortisol and other clinical and biochemical parameters , which are relevant in stroke. Significant

correlation was observed between serum cortisol and various parameters like systolic blood pressure , diastolic blood pressure , total count and admission blood sugar level ($P<0.001$). The study done by Slowik A, Turaj W, et al.(2002)[5] had shown that elevated cortisol levels in acute stroke is related to markers of inflammatory response like total WBC count which was evident in our study also.

We further proceeded with computing correlation coefficient for these parameters and was found that highest level of correlation existed between admission blood glucose level and serum cortisol values (Correlation coefficient 0.748). Least level of correlation was observed with diastolic blood pressure (Correlation coefficient 0.337) . Similar correlation was also observed between SSS score and these parameters. This is in concordance with earlier studies, like that conducted by cardiovascular and medical sciences division of University of Glascow that showed blood glucose is related significantly to stoke severity.

The study done by Murros K, Fogelholm R, et al.(1993) had also shown that serum cortisol value correlates with blood glucose in stroke patients[3].

We also evaluated the relation between serum cortisol and functional outcome in stroke . The study conducted by Department of Endocrinology, University Hospital,Basel,Switzerland , which was published in Endocrine Abstracts (2009) concluded that cortisol is a

prognostic marker to predict functional outcome and mortality in patients with acute stroke .we estimated the functional outcome after a period of 3 months , by calculating Barthel Index and Modified Rankin Score . Barthel Index ranges from 0 to 100 . Lower the score , more poor the functional outcome . Our study showed statistically significant correlation between serum cortisol and Barthel Index at the end of three months($P<0.001$) . It was observed that patients with higher serum cortisol values have low Barthel Index at the end of three months and hence poor functional outcome .

Modified Rankin Score (MRS) ranges from 0 to 6 , higher score indicating poorer outcome . MRS score of 6 indicates death . Our study showed statistically significant correlation between serum cortisol and Modified Rankin Score (MRS) at the end of 3 months ($P<0.001$).

Patients with higher cortisol values at admission were having higher Modified Rankin Score at the end of 3 months , indicating poor functional outcome . All the patients who died had high serum cortisol levels ie greater than 34 mcg/dl . [reference range 3.09 – 16.66 mcg/dl] The limitation of our study was that ACTH, nor-adrenaline , adrenaline and other hormones involved in the stress response were not measured .

CONCLUSION

Following conclusions were derived from our study

1. High serum cortisol correlated with severity of stroke as evidenced by an inverse relation with SSS . As serum cortisol level increases SSS score decreases .
2. High serum cortisol also correlated with systolic blood pressure , diastolic blood pressure , total count and admission blood sugar level . The highest correlation coefficient was observed with random blood sugar level at admission and the lowest was for diastolic blood pressure . This shows that admission blood sugar level correlates well with serum cortisol and hence with stroke severity .
3. Serum cortisol is a prognostic marker to predict functional outcome and mortality in patients with stroke. This is evidenced by high correlation between serum cortisol and indices of functional outcome like BI and MRS at the end of three months .

SCOPE FOR FUTURE STUDIES

This study which was conducted in Indian population has significant observations and potential therapeutic implications as well. Still few more questions remain unanswered. Although serum cortisol has been convincingly proved an independent indicator of severity and functional outcome in stroke, the exact pathophysiological mechanism of this relationship has to be elucidated by further studies. It is also not understood whether elevated serum cortisol levels in itself is beneficial or detrimental in acute stroke .

Estimation of other hormones involved in stress response such as ACTH, epinephrine, norepinephrine and cytokines can be undertaken to correlate the severity of stroke.

PROFORMA

Name:

Age & Sex

IP No DOA: Address;

Ph :

Time duration:

Presenting complaints:

LOC: Seizures: Fever: Others:

Past History

HTN DM PT BA IHD CVA

Seizures

Personal history

Smoking Alcoholism

General Examination

BP: pulse RR JVP: Temperature:

CVS

RS

GIT

CNS

INVESTIGATIONS:

CBC:

Blood

Sugar:

Urea:

Creatinine:

Electrolytes:

Urine

- Sugar
- Albumin
- Deposits

ECG

CXR

Lipid profile

Serum cortisol

CT Brain:

SSS

1. Consciousness
2. Orientation
3. Speech
4. Eye movements
5. Facial palsy
6. Gait
7. Arm power
8. Hand power
9. Leg power
10. Foot paresis

THE BARTHEL INDEX [BI]

	At discharge	**1month**	**2 month**	**3 month**
BI				

MODIFIED RANKIN SCORE [MRS]

	At discharge	1month	2 month	3 month
MRS				

MASTER CHART

S.No	Ip no.	Name	Age	Sex	HTN	T 2 DM	SMOKING	ALCHOHOLIC	SBP	DBP	TC	RBS	CORTISOL	CT SCAN	SSS	BI			MRS		
																0	1	3	0	1	3
1	39724	Murugan	80	M	Y	N	Y	N	140	100	12000	138	10.26	Hge Lt parietal lobe	41	55	80	90	3	3	2
2	41039	Babu	75	M	Y	Y	Y	N	180	100	14000	186	28.46	Massive Lt MCA Infarct	15	20	35	45	5	4	3
3	40906	Mariappan	70	M	Y	N	Y	N	150	100	9200	102	11.38	Rt MCA infarct	40	50	75	85	4	3	2
4	37653	Karuppasa	90	M	Y	Y	N	N	140	100	11000	148	25.32	Hge Rt thalamus	20	20	35	45	4	3	3
5	45924	Joseph	55	M	Y	N	Y	N	200	120	14000	182	42.36	Rt IC Hge with ventricular ex	4	5	0	O	6	6	6
6	56237	Sethuamm	49	F	Y	N	N	N	140	90	7300	104	17.69	Hge Lt PUTAMEN	30	40	55	60	4	3	3
7	6822	Kurunthan	65	M	Y	Y	Y	Y	160	90	9600	152	21.42	Lt MCA infarct	25	25	40	55	4	3	3
8	59915	Sankaramr	67	F	N	N	N	N	200	120	13400	152	19.64	Rt MCA infarct	20	35	45	55	4	4	3
9	56162	Srinivasan	85	M	Y	N	Y	N	190	100	14000	172	29.46	Lt Basal ganglia Hge	8	15	25	35	5	4	4
10	56748	Sakthivel	60	M	Y	N	Y	N	170	100	9000	132	15.62	Lt MCA infarct	24	40	65	75	4	3	2
11	53537	Kandan	53	M	Y	N	Y	N	160	100	7000	92	8.68	Lt Parietal Hge	45	40	65	85	3	2	2
12	49667	Gomathi	85	F	N	N	N	N	180	100	7600	123	16.33	Hge Rt Putamen	30	40	60	75	4	3	2
13	48447	Ramalinga	62	M	Y	N	Y	N	150	90	6200	96	5.96	Rt parieto occipital infarct	44	40	70	90	3	2	1
14	45922	Velmayil	40	F	N	N	N	N	150	100	10200	133	18.24	Hge Lt thalamus	30	40	70	80	4	3	2
15	39788	Muthulaks	80	F	N	N	N	N	130	80	6100	88	8.16	Rt frontal infarct	40	40	60	70	3	2	2
16	43988	Rajapandi	60	M	Y	N	Y	N	140	90	12000	124	12.88	Lt MCA infarct	32	30	50	65	4	3	2
17	68178	Ayyadurai	84	M	Y	N	Y	N	200	110	16800	182	35.14	Massive Lt MCA Infarct	8	15	25	35	5	4	3
18	68322	Mathan	67	M	Y	N	N	N	150	90	7000	131	14.56	Rt MCA infarct	31	30	50	60	4	3	2
19	14428	Pakkiyalak	50	F	Y	N	N	N	190	100	14000	140	31.74	Rt IC Hge with ventricular ex	9	15	25	35	5	4	3
20	7476	Sumithra	47	F	N	N	N	N	140	90	7900	132	14.58	infarct Rt ACA territory	29	30	50	60	4	3	2
21	66926	Mohamme	45	M	Y	N	N	N	160	90	6100	96	13.44	Hge Lt parietal lobe	29	30	50	65	4	3	2
22	34243	Nallaiyan	50	M	N	N	N	N	130	90	6400	111	10.96	Rt MCA infarct	37	35	55	75	3	2	1
23	56723	Muthumar	70	F	Y	Y	N	N	160	100	6700	121	10.16	Lacunar infarct Lt MCA	39	35	65	80	3	2	1
24	16428	Arumugam	68	M	Y	Y	Y	Y	180	100	9400	162	29.94	Hge Rt Parietal lobe	13	20	30	40	4	3	3
25	10575	Sankar	52	M	Y	Y	Y	Y	140	90	9500	105	12.76	infarct Rt MCA&PCA territor	29	30	50	60	4	3	2
26	7476	Balagurusa	60	M	Y	Y	N	N	200	100	8900	135	16.74	Hge Rt Thalamus	27	25	45	60	4	3	3
27	9244	Karuppay	55	F	N	N	N	N	190	100	9600	148	16.32	Rt Capsuloganglionic infarct	30	30	50	60	4	3	2
28	57619	Annammal	65	F	Y	Y	N	N	160	100	8400	154	14.48	Rt parieto occipital infarct	27	30	50	65	4	3	2
29	38342	Shahul Har	57	M	N	Y	N	Y	150	100	9200	162	23.44	Rt MCA infarct	20	20	35	45	4	3	3
30	35501	Subramany	43	M	Y	Y	N	Y	150	100	9000	167	15.94	Hge Lt frontoparietal region	25	25	45	60	4	3	2
31	35671	Lkshmanar	55	M	Y	Y	Y	Y	200	100	18600	182	41.16	Rt IC Hge with midline shift	4	5	0	0	5	6	6
32	33026	Ganapathi	68	M	N	Y	N	Y	190	100	11000	170	36.93	Massive Rt MCA Infarct	8	5	15	25	5	4	3

33	37586	Beer Myde	85	M	N	Y	N	N	170	90	9900	164	14.18	Lt MCA infarct	30	30	45	60	4	3	2
34	31534	Vairamani	47	M	Y	Y	N	N	150	90	9200	128	12.64	Infarct Lt MCA/PCA	30	30	50	65	4	3	2
35	31513	Subash Ch	48	M	Y	Y	N	Y	160	100	7600	126	11.82	Lt MCA infarct	34	35	50	70	3	3	2
36	29858	Thangaraj	55	M	N	N	Y	Y	180	100	6900	88	6.68	Lacunar infarct Lt MCA	47	40	75	90	3	2	1
37	29956	Ganesan	45	M	Y	Y	Y	Y	140	100	9300	137	15.43	Lt Capsu oganglionic infarct	25	25	45	60	4	3	2
38	28334	Velu	58	M	N	N	N	N	140	80	8900	104	34.82	Rt MCA infarct	34	40	70	80	4	3	2
39	56196	David Dani	70	M	Y	N	Y	Y	180	100	17400	156	19.15	Rt MCA infarct	21	35	55	70	4	3	3
40	44748	Kali	47	F	Y	N	N	N	130	80	7200	110	9.16	Cerebellar infarct	44	55	75	85	3	2	1
41	47171	Thangavel	75	M	Y	N	Y	N	180	100	14200	152	34.44	Lt MCA infarct	18	15	30	40	5	4	3
42	48227	Pauldurai	72	M	N	Y	Y	Y	160	110	8000	102	4.34	Lt Parietal Infarxt	47	55	75	90	3	2	1
43	45989	Valli	65	M	Y	N	N	N	180	100	8300	107	14.14	Lt MCA infarct	30	40	70	80	4	3	2
44	17044	Manickam	66	M	Y	Y	Y	Y	150	90	12700	98	12.98	Rt MCA infarct	32	45	75	85	4	3	2
45	39724	Manikanda	67	M	Y	N	N	Y	160	110	12500	136	13.98	Rt MCA infarct	32	25	50	75	4	3	2
46	14122	Komu	76	M	Y	Y	N	N	200	120	19100	201	34.18	Rt IC Hge with midline shift	6	10	0	0	5	6	6
47	11103	Velsamy	45	M	N	N	Y	Y	150	100	8800	98	2.36	Lt MCA infarct	50	45	75	95	3	2	1
48	39688	Balasubran	53	M	Y	Y	Y	Y	170	100	8700	136	19.34	Hge Lt capsuloganglionic	24	35	60	70	5	4	3
49	47129	Paulraj	62	M	N	N	N	N	140	100	7300	106	8.36	Lt high parietal infarct	44	40	65	80	3	2	1
50	47277	Thangavel	70	M	Y	Y	N	N	180	100	13600	177	23.46	Lt MCA infarct	24	35	55	65	4	3	2

KEY TO MASTER CHART

DM - Diabetes Mellitus

HTN - Hypertension

SBP - Systolic Blood Pressure

DBP - Diastolic Blood Pressure

TC - Total Count

RBS - Random Blood Glucose

Hge - Haemorrhage

Lt - Left

Rt - Right

IC - Intracerebral

MCA – Middle Cerebral Artery

ACA - Anterior Cerebral Artery

PCA - Posterior Cerebral Artery

SSS – Scandinavian Stroke Scale

BI - Barthel Index

MRS - Modified Rankin Score

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A STUDY ON CORRELATION BETWEEN SERUM CORTISOL AND EARLY STROKE OUTCOME

ABSTRACT

INTRODUCTION

It is a well established fact that cerebrovascular accident is an acute stressful event . There is a surge of inflammatory mediators following a stroke . Not much studies have correlated these inflammatory or stress response following stroke with the severity and outcome of stroke .

AIM OF THE STUDY

The aim of our study was to find out any correlation between serum cortisol at the time of admission with the severity of stroke as well as functional outcome at the end of three months . We also tried to correlate serum cortisol with other clinical and paraclinical parameters like blood pressure , total count and admission blood glucose level.

MATERIALS AND METHODS

Study included 50 patients admitted within 24 hours of onset of stroke . Severity of stroke was assessed at admission by Scandinavian stroke scale . Systolic and diastolic blood pressure were recorded in all patients . Blood was taken for total count ,random blood glucose and serum cortisol . A single admission cortisol measurement was chosen since the diurnal variation in

cortisol secretion is lost in stroke . Functional outcome was assessed by barthel index and modified rankin score at discharge , 1month and at the end of 3 months . Data was plotted in a master chart and statistical analysis was made .

RESULTS AND OBSERVATIONS

The average serum cortisol level was 18.43mcg/dl [reference range 3.09-16.66mcg/dl] . Serum cortisol level was higher in male patients, patients with haemorrhagic stroke and in those aged above 60 years.Statistically significant correlation was observed between serum cortisol and Scandinavian stroke scale. ($p<0.001$). Patients with higher serum cortisol level at admission had more severe stroke . Serum cortisol also showed significant correlation with indices of functional outcome like bathel index and modified rankin score , indicating poor functional outcome at the end of three months in patients who had high cortisol values . A positive correlation was also seen between cortisol and systolic blood pressure, diastolic blood pressure , total count and admission blood glucose level . The highest level of correlation was observed between cortisol and admission blood glucose level ,correlation coefficient being 0.748 . All three patients who died had very high cortisol level (>34mcg/dl)

CONCLUSION

High serum cortisol value at admission correlates with severity of stroke. Positive correlation exists between serum cortisol and systolic blood pressure ,

diastolic blood pressure , total count and random blood glucose at admission. High serum cortisol is a prognostic marker for functional outcome and mortality in stroke .

KEY WORDS

Scandinavian stroke scale , barthel index , modified rankin score , early stroke outcome , serum cortisol